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EXPERIMENTAL AND SPONTANEOUS SCHWANNOMAS (PERIPHERAL GLIOMAS)*

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INTRODUCTION

The following pages are addressed to that minority of pathologists who still refuse to admit that the fundamental constituent of the encapsulated tumors of the peripheral nerves is the schwannian syncytium, a neurectodermal structure, and not the mesodermal fibroblast. The great majority of pathologists who follow Bard, Durante, Francini, Verocay, Antoni and many others in accepting these tumors as schwannomas will not object to my reopening the discussion by offering new evidence to confirm their views. Let us first summarize the arguments advanced by the partisans of the connective tissue hypothesis and by those of the schwannian hypothesis as to the origin of these tumors.

The reasoning of the first group appears to be quite logical. The tumor cells are branched, anastomosing by their processes like connective tissue cells. They give rise to many fibrils which react like collagen or like reticulin and which are arranged like the fibers of the endoneurial framework. Furthermore one may distinguish delicate fibrils staining blue with Mallory's phosphotungstic acid hematoxylin, identical with the "fibroglia fibrils" of fibroblasts. These advocates assume that only fibroblasts, mesodermal cells, are capable of producing collagen and fibroglia fibrils. These tumors of the peripheral nerves should therefore be fibroblastomas (Pen-

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field's perineurial fibroblastoma) and they cannot arise from Schwann cells, the neurectodermal nature of which is no longer open to discussion.

The following observations favor the second opinion. In certain examples of generalized neurofibromatosis, studying nerves of apparently normal dimensions, several authors (Verocay, Pick and Bielschowsky) have seen microscopic tumors composed of Schwann cells in proliferation. In the beginning this schwannian proliferation is accompanied by budding of collateral neurites. This budding of collaterals soon ceases but the multiplication of Schwann cells continues, accompanied by connective tissue proliferation. The specific cells of these tumors are connected in a syncytium like Schwann cells; they possess elongated nuclei of the same structure as schwannian nuclei, and they are grouped in networks, in bundles and in palisades. These latter structures are pathognomonic; they have only superficial resemblance to the groupings found in certain myomas and fibroblastomas. Between the cells there are fibers of peculiar nature and staining, coloring orange or pale pink with Van Gieson's stain.

Up to this point there is almost complete unanimity. The differences of opinion begin when assessing the importance of connective tissue participation in the formation of these tumors. While some hold it to be minimal, others believe it to be dominant or rather progressively dominant, increasing in proportion as the neurinoma grows larger. Following Verocay, Pick and Bielschowsky state that the growth of the endoneurial and perineurial connective tissue tends to disperse and stifle the Schwann cells and that they become as difficult to distinguish as the cancer cells of certain scirrhous tumors of the breast or of the stomach (!). According to Pick and Bielschowsky, the place of these tumors in the classification can be determined with certainty only by studying the initial changes.

The heart of the argument advanced by the first group is the presence in these tumors of collagen fibers of endoneurial type. They assume the connective tissue nature of the cells which, having produced the fibers, continue to live among them. For the second group these fibers create a difficulty. They extricate themselves by assigning the fibers to the connective tissue stroma of the schwannoma, a stroma of endoneurial origin, which to a greater or less extent may replace the neurectodermal cells and mask them if not

stifle them altogether, so that in the end a neurofibroma may become a more or less pure fibroma.

It must be conceded that the schwannian nature of the tumor cells has not been demonstrated clearly. The nuclei have been described accurately by many pathologists, but the features noted are not sufficiently characteristic to be regarded as specific and belonging only to schwannian nuclei. The features of the cytoplasm are wholly lacking in precision and one cannot see clearly how they differ from those of fibroblastic cytoplasm. From this point of view the opposition of certain pathologists to the neurectodermal hypothesis of encapsulated neurofibromas is justified.

Various circumstances have led me to support the schwannian conception of neurinoma. The friendship with which Professor Jean Nageotte has long honored me has permitted an intimate acquaintance with his work on the peripheral nerves and particularly on the schwannian syncytium, to which, following Held, he justly gives the name of peripheral neuroglia. Not only have I been able to verify all that Nageotte has written of the schwannian syncytium, but also I have been able to make new observations on experimental specimens that he prepared for me with the collaboration of Mlle. Guyon, and which I have treated by my own methods. Finally, certain exceptionally favorable specimens of human neurinomas and then all of the neurinomas in my collection, studied with these methods, have convinced me that these tumors are constituted almost exclusively of Schwann cells and that the connective-vascular tissue enters into their constitution to the same extent as it enters into the constitution of central gliomas, no more and no less.

In the present paper I shall describe the normal syncytium of Schwann according to Nageotte. I shall then consider its characteristics, when stimulated to autonomous proliferation and to the production of experimental schwannomas. In Part II I shall apply these observations to the study of human neurinoma.

Part I

EXPERIMENTAL SCHWANNOMAS

The Schwannian Syncytium. The Schwann Cell

Nowadays I believe everyone accepts the medullary origin of the Schwann cells, their departure from the neural crest and their migration along the primitive bundles of axones. In the adult medullated nerve fiber each internodal segment is enclosed in a delicate protoplasmic envelope, bounded externally by a cuticle — the membrane of Schwann. The protoplasmic envelope is applied closely to the myelin sheath and presents slight annular thickenings corresponding to the Schmidt-Lantermann incisures. In the middle of each internodal segment there is a slight thickening of the protoplasmic envelope. This thickening contains an oval nucleus with fine chromatin network. From this median thickening and at either end of the nucleus, one or two narrow, linear thickenings or ribs run in a longitudinal direction and they soon bifurcate. Near the nodes these ribs are connected by similar oblique and transverse thickenings, constituting Nageotte's marginal plexus.

The marginal plexus ends in a sort of protoplasmic collar around the node. The protoplasmic ribs of adjoining segments end in this collar. The collar represents a line of continuity between two nucleated segments of the schwannian syncytium and not a line of separation between two independent Schwann cells. Nageotte has shown that the rings revealed by Ranvier's application of silver nitrate to the fresh nerve have the same value as the black lines that outline the peritoneal endothelia, when treated similarly with silver nitrate. They mark a superficial boundary between two nucleated territories but they do not interrupt their deep continuity.

The medullated axone, then, is enclosed in a continuous and multinucleated syncytium provided with linear thickenings which anastomose in plexuses. The portion of the syncytium corresponding to an internodal segment possesses a single nucleus. It is this ensemble, the segment of the syncytium with its nucleus, that goes by the name of Schwann cell. The Schwann cell is a physiological unit but anatomically it is continuous with adjoining segments in an unbroken syncytium.

Endoneurium and Membrane of Schwann

The endoneurium is generally accepted as a connective tissue, an assemblage of collagen and reticulin fibrils together with branching cells, all of mesodermal origin. I shall accept this postulate provisionally, although it is open to discussion. Two kinds of fibers go to make up the fibrillar endoneurium.

1. A system that I shall call interstitial, occupying the angular space where three medullated fibers meet. This interstitial system is composed of fibers running parallel with the nerve, branching, perhaps anastomosing with one another. Van Gieson's solution stains them faintly; aniline blue of the trichrome stain shows them clearly; silver methods impregnate them intensely. These interstitial argyrophil fibers correspond to the networks of Key and Retzius, and of Cajal. In their interstices are found the endoneurial cells, of spongy cytoplasm, elongated in the direction of the nerve, their branches anastomosing with those of adjoining cells.

2. A fibrillar sheath first demonstrated by Plenk and well described by Laidlaw. This sheath consists of delicate argyrophil fibrils, seen best after fixation in Zenker's fluid. The fibrils are circular, oblique and longitudinal. They anastomose to form a web or net which is applied closely to the Schwann cell. They are continuous with the longitudinal fibers of the interstitial endoneurium. In brief, the schwannian syncytium is enclosed in a web of reticulin resembling that which surrounds the epithelial lining of the intestinal glands, and, like the latter, it is a basement membrane.

When a cross-section of a nerve is impregnated by Laidlaw's silver method and counterstained by ponceau-acid fuchsin followed by light green, the result is very curious. Each nerve fiber is enclosed in a delicate black ring of reticulin which is closely applied to the schwannian cytoplasm. The cuticle of the membrane of Schwann is invisible. This should be taken in connection with Laidlaw's interesting demonstration in the roots of the spinal nerves, that the membrane of Schwann and the Plenk-Laidlaw argyrophil sheath accompany the root fibers into the marginal glia to the same point. These two structures have exactly the same distribution. They are closely connected, therefore, and seem even to be included one within the other. One may ask whether they are not one and the same thing. Presently we shall see the importance of this conception.

Artificially Stimulated Proliferation of the Schwannian Syncytium

Section of a medullated nerve is followed immediately by wallerian degeneration of its fibers. In the proximal stump the degeneration is limited to the tip; it extends through the entire length of the distal stump. Wherever it exists, the degeneration is accompanied (fourth day) by mitotic proliferation of the schwannian nuclei (Büngner). As a result of this proliferation, schwannian sprouts invade the wound both from the proximal and from the distal stump, and they approach each other and finally unite (Nageotte). The neurites of regeneration coming down from the upper stump travel in the corresponding schwannian sprouts; together they constitute Nageotte's neuroglioma. The purely schwannian sprouts coming up from the lower stump construct a schwannoma (Nageotte's peripheral glioma) which, after its union with the central neuroglioma, is in its turn invaded by the descending neurites. Guided by the schwannian bands, the neurites soon gain the blighted fibers of the distal stump and repopulate them. On the arrival of the neurites in the schwannian syncytium its proliferation ceases immediately.

Experimental Schwannomas

Nageotte's Experiments

If, as Nageotte has done, we prevent innervation of the distal stump by tearing out the proximal end of the nerve together with its roots, the peripheral schwannoma grows for a long time and its fibers hypertrophy. Reduced to their syncytium, the fibers of the distal stump hypertrophy also. We shall see that these hypertrophies correspond not only to a volumetric increase of the syncytium (Nageotte), but also to an amitotic proliferation of its nuclei.

Proliferation of the schwannian syncytia is still more pronounced if, after cutting the sciatic nerve of a rabbit and tearing out the proximal end, together with its roots and ganglia, an incision is made through the distal stump about 1 cm. below the first incision; the piece of nerve is left in place. In this way an isolated piece of nerve is deprived of its circulation temporarily (Nageotte). The fragment of the nerve shortens. From each end of its contracted perineurial casing there protrudes a hemispherical hernia consisting

of endoneurium and the ends of the nerve fibers. On the conclusion of wallerian degeneration and revascularization of the endoneurium, these damaged nerve fibers, reduced to their syncytia, undergo gigantic hypertrophy. Schwannian sprouts emerge and, together with the regional connective tissue, construct a fibroglioma at each end of the fragment. The one, situated between the fragment and the distal stump, unites with a similar fibroglioma arising from this stump; together they constitute an aneuritic cicatrix very similar to an innervated cicatrix. The other fibroglioma, springing from the proximal end of the fragment, becomes an enormous tumor which invades the neighboring muscles and is still growing after five months.

Into this experiment, which I shall designate as Experiment I and which resembles one already made by Bethe, there may creep a source of error. Neurites coming down from the spinal orifices or elsewhere may repopulate some of the schwannian bands, myelinize them and create an illusion of autogenous regeneration. In another experiment, which I shall call Experiment II, Nageotte and Guyon prevented any intrusion of this kind. From the right sciatic nerve of a rabbit they excised a piece 1 cm. long and transplanted it alongside of the left sciatic nerve of the same animal, separating the gluteal muscles without cutting them. From each end of the graft there grew a schwannian tumor which adhered to the neighboring tissues. In three months' time such a tumor may have acquired twenty times the volume of the original graft and still be growing after five months.

These tumors are exactly like those observed after the simple section of the nerve in Experiment I. They demonstrate the remarkable fertility of the schwannian syncytium, when deprived of the control exercised by the neurites. Both tumors are of capital interest to us in that they enable us to fix precisely the characteristics and properties of the schwannian syncytium when in autonomous proliferation.

Nageotte and his collaborator, Mlle. Guyon, repeated these experiments with admirable results and presented me with some remarkable specimens which required only to be cut, stained and studied. For any interest aroused by the present work, the reader is indebted to them; if it should be judged mediocre or worse, it is to me alone that criticism should be directed. I shall make use only

of those pieces that were excised after three months' growth, fixed in Bouin's picro-formol, embedded in paraffin and cut in serial sections, both transverse and longitudinal. The stains used were the trichrome (derived from Mallory's connective tissue stain); Laidlaw's silver stain for reticulin, either alone or followed by ponceau-acid fuchsin and light green; and Mallory's phosphotungstic acid hematoxylin.

Since similar pieces have already been studied by Nageotte, I shall again be obliged to draw on his descriptions. Those who, like me, have studied subjects already treated by him will soon learn how little there is left to glean after this great observer. It so happens, however, that the little which I am able to add to his observations is of decisive importance for the schwannian hypothesis of neurinoma.

The Distal Segment

With this name I designate the fragment of the distal stump that has been cut and left in place, as in Experiment I. This piece of nerve is relatively slender, having lost about one-fourth of its original caliber. Its fibers are degenerated and swollen here and there by fatty ovoids not yet absorbed. In the intervals between the ovoids the fibers have a uniform caliber; they are geometrically perfect cylinders. This does not mean that all fibers have the same diameter. Some are broad, some narrow. It is probable that the caliber of each degenerated fiber depends on its original caliber before degenerating.

On cross-section the fibers are seen to be notably broader than in the days immediately following wallerian degeneration; they have undergone Nageotte's secondary hypertrophy. The fibers are separated from one another by abundant endoneurial collagen, very dense and of sclerous aspect. Each fiber is surrounded by a dark blue, circular sheath (aniline blue of the trichrome stain) closely applied to it. At first sight this sheath appears to be homogeneous but it is really composed of longitudinal fibrils pressed closely against one another like the staves of a barrel. The fibrils may be detected in cross-sections where a defect in the knife has pulled them apart a little. In longitudinal sections they outline a blue striation on the surface of each nerve fiber.

With Laidlaw's silver method, these fibrils impregnate indis-

tinctly. They are violet and not black. They run almost exclusively in a longitudinal direction and are much coarser than the argyrophil fibrils that run in all directions and envelop the normal nerve fiber as in a net or web. They are continuous with the interstitial fibers of the endoneurium. These latter fibers seem to be no more numerous than those of the normal endoneurium, but they are broader and their colorability with aniline blue and by the Van Gieson method has increased to the detriment of their argyrophilia. The endoneurial cells have undergone no appreciable change.

In a word, the entire endoneurial interstitial substance has become denser and collagenized. The original argyrophil reticulum has been replaced by a coarse, sclerous, collagenous network. It is fitting to recall here the remarkable property possessed by this fundamental substance of the sclerous endoneurium, of swelling in weak solutions of nitric acid. This property is confined to this tissue and to the collagen of the cornea (Nageotte).

The degenerated nerve fibers color pink in acid fuchsin. No fuchsinophil membrane comparable to the primitive membrane of Schwann separates them from the collagenous sheath. It seems as if the latter, which has replaced Laidlaw's reticulin membrane, has at the same time replaced the membrane of Schwann. Is not this an argument in favor of the idea that the reticulin membrane and the membrane of Schwann are one and the same thing?

In cross-sections the degenerated fibers enclosed in their collagen tubes seem to consist of two substances, a homogeneous fluid faintly colorable by fuchsin and tiny angular bodies of various sizes, some punctiform, others larger and staining more deeply. In some of the larger bodies there is seen a round nucleus. In longitudinal sections there are protoplasmic bands regularly calibrated and set with many oval elongated nuclei with delicate reticular chromatin and often containing a large plasmosome. The cytoplasm appears to be striated longitudinally. In reality this striation corresponds to the juxtaposition and to the fasciculation of slightly sinuous cell bodies, together with their branches running lengthwise along Büngner's bands. Conforming to Nageotte's conception, a Büngner band consists of stellate cells with filiform prolongations anastomosing in a network, the meshes of which are drawn out lengthwise.

In brief, this syncytium reproduces the essential reticular and anastomotic arrangement of the schwannian syncytium of the

medullated fiber; but each territory corresponding to a former internodal segment now possesses several nuclei and several stellate cytoplasmic bodies, anastomosing with one another and with those of adjoining segments which have multiplied similarly. Since the axis cylinder and the myelin sheath have disappeared, the schwannian syncytium occupies the entire thickness of the fiber and not merely the periphery. It is cortical only around the fatty ovoids.

To these observations, which conform exactly to those made by Nageotte, I should add another. The schwannian nuclei of the hypertrophied syncytium are more numerous than those of the fiber when recently degenerated and reduced to a filiform band. The nuclei often present longitudinal fissures of varying depth; or two or three elongated nuclei are found side by side in close contact in the same cytoplasm. It is obvious that these groups result from amitotic division and longitudinal cleavage. At other points the nuclei, still near one another, are ranged in an oblique line but in different axial planes of the initial cylinder, as if the nuclei of an isogenic group had slipped past one another, together with their respective cytoplasms, and were spacing themselves regularly along the degenerated fiber. This disposition is rare in the distal stump but becomes more frequent near the cut end of the nerve. I shall return to it later. This proliferation in the heart of a nerve that is unable to elongate is a curious phenomenon. It explains the secondary hypertrophic broadening of Büngner's bands, a broadening not due solely to volumetric increase of the Schwann cells but also to their amitotic multiplication, to their hyperplasia.

Segment (Experiment I) or Graft (Experiment II)

The events in these two pieces are essentially the same. For purposes of description either may be chosen. I have already described the shortening of the piece of nerve when simply isolated (Experiment I), or when isolated and then transplanted (Experiment II). I have noted also the hernia of its contents, the endoneurium and nerve fibers, protruding beyond the divided perineurium. An edema infiltrates the entire piece, affecting both its endoneurial contents and the perineurium, the collagenous laminae and endothelia of which separate, leaving between them large lacunae filled with an absolutely colorless fluid. By isolating the elements of the nerve, the edema enables us to follow them more easily in serial

sections and greatly facilitates histological analysis. The edema is much more pronounced in the segment that is simply cut and left in place (Figs. 1 and 3) than in the graft (Fig. 10). For this reason in this description I shall use chiefly the specimens of Experiment I. To avoid prolonging this paper beyond measure, I shall limit myself to a synthetic statement: for analysis the reader is referred to the figures and to their copious legends.

The phenomena that I am about to describe begin at each end of the incised segment and extend progressively to the middle of it, so that by studying first the nerve fibers and the endoneurium in the middle of the segment and then toward either end, we may reconstitute the successive stages of their transformation.

The Schwannian Bands (Diagram)

Secondary hypertrophy of the degenerated fibers, already distinct in the distal stump, assumes enormous proportions in the incised segment. If we should designate the mean diameter of the distal bands by the figure 1, their diameter in the middle of the segment would be from 4 to 10 (Fig. 1) and near the ends from 10 to 20 (Fig. 2). This broadening of the original fiber is accompanied by active amitotic proliferation of its nuclei. It is followed by longitudinal cleavage which converts each schwannian band into a bundle identical with the innervated bundle of regeneration, except that it possesses neither neurites nor myelin.

We shall follow the steps of this transformation. Our point of departure will be the reticular syncytium enclosed in a thick collagenous sheath formed of coarse, closely-set, longitudinal fibers which have replaced the former membrane of Schwann and the Plenk-Laidlaw reticular sheath.

The schwannian cytoplasm fills the collagen sheath completely; at this point there is no fluid between the tissue elements. The cytoplasm is pale pink, vitreous and homogeneous. Cross-sections (Fig. 1) show it to be divided into polygonal territories of unequal dimensions by very thin septa of darker red color. The septa are dotted with tiny points still darker red; these are cross-sections of delicate fibrils. Here and there a slight retraction, a shrinking of certain territories, shows that each of them is bordered by a thin membranous condensation. It is obvious that the protoplasmic septa between contiguous territories are very thin membranes, each

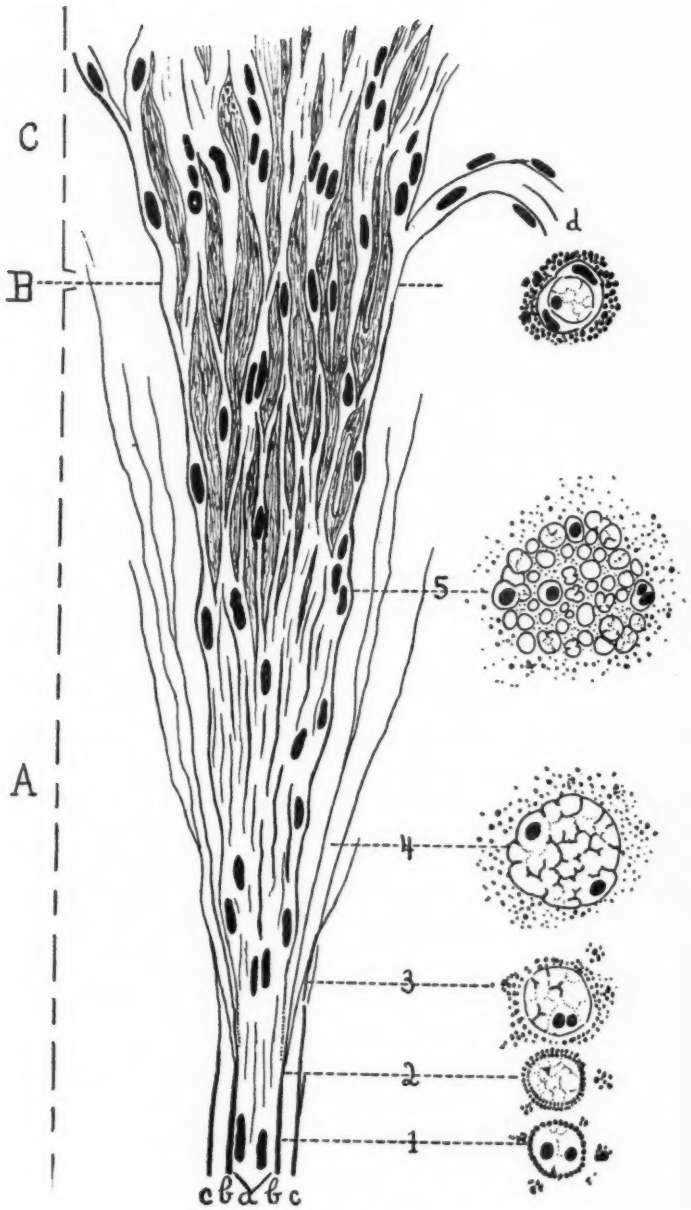


DIAGRAM 1

of them closely adherent to its cytoplasmic territory but susceptible of separation. These are the membranes of Schwann, forming around each of the territories that have arisen from a single Schwann cell. The broader territories often contain a nucleus. Here and there are cross-sections of several nuclei, two, three or more in the same fiber.

In longitudinal sections (Fig. 3) these fibers appear to be striated. The striation corresponds to different shades of color of the cytoplasms that are elongated in the direction of the fiber, of the membranous septa which separate them, and of the tiny fuchsinophil fibrils lodged in the septa.* The striation ceases or diminishes in the

* After fixation in picro-formol, phosphotungstic acid hematoxylin stains these fibrils and these septa bluish. It is probable that the fibrils correspond to those which Nageotte demonstrated with Benda's neuroglia stain.

DIAGRAM 1

Experiment II. Transformation of a degenerated fiber into an aneuritic bundle of regeneration.

(A) Incised segment. (B) Limit of the hernia. (*a*) Degenerated medullated fiber reduced to its schwannian syncytium and hypertrophied secondarily. (*b*) Its collagen sheath. (*c*) Interstitial endoneurium dissociated by edema.

(1 to 5) Successive aspects of the fiber at different levels. On one side a longitudinal section; on the other a cross-section.

(1) Two isogenic nuclei. Incomplete cytoplasmic partitioning. The collagen sheath is a little distended by its contents. Its longitudinal fibrils are slightly separated from one another.

(2) Internuclear region. Cytoplasmic partitioning (dots in cross-section, delicate lines in longitudinal section) is more advanced here than in the region of the nuclei. The laminae of the collagen sheath begin to separate.

(3) Beginning of collagenous partitioning. The old collagen sheath of longitudinal fibers has separated from the schwannian cylinder and is being incorporated into the interstitial endoneurium. The cylinder itself is covered by a new reticular sheath, chiefly of circular fibrils (dots in longitudinal section) which gradually grows more dense.

(4) Collagenous partitioning is being completed, the collagen replacing the cytoplasmic septa.

(5) Cleavage of the collagenous septa and isolation of the young cylinders. Between them is the neo-endoneurium, the framework of which is constituted by longitudinal fibrils liberated from the septa at the time of their cleavage.

(C) Infiltrating schwannoma. Cylinders continuous with those of an aneuritic bundle invading the connective tissue. Isogenic nuclear groups on the same transverse plane or in process of shifting along the cylinder.

(*d*) Schwannian cylinder in the stage of cytoplasmic partitioning invading the connective tissue. It passes through the same stage of partitioning as the original cylinder. It is separated from the surrounding tissue by an endotheliform perineurium, formed probably by cells emigrated from the endoneurium of the incised segment and not by local connective tissue cells.

vicinity of the nuclei. These nuclei are elongated ovals, sometimes gigantic, containing a large plasmosoma, often fissured longitudinally. Isogenic groups of two or three nuclei are often seen.

Around these broadened fibers the collagenous sheath is distended. Its longitudinal fibers are no longer contiguous, but separated from one another by the swollen contents. Fine collagen and argyrophil (Laidlaw's method) fibrils soon appear in the septa. Some of them are continuous with fibers of the perineurial sheath; others are axial without visible continuity with any preformed collagen. Still other fibrils are added to the first group and little by little each cytoplasmic septum (red) is replaced by a collagenous septum (blue). The partitioning is more precocious at the periphery of each fiber than in its center, so that at a certain stage a cross-section of a fiber gives the appearance of peripheral spurs projecting inward. The spurs are the beginnings of radial septa.

When the collagenization of the membranes of Schwann is finished, each cell (nucleated body together with its multiple and anastomosing branches) of the syncytium is enclosed in a continuous tubular sheath, retiform like the cell and moulded exactly on it (Figs. 2, 3 and 4). Later the party walls split so that there comes to be an individual sheath around each fiber (Figs. 2, 6 and 8). In this way two cytoplasmic branches, locally distinct but contiguous, may separate from each other, each enclosed in its collagen sheath, which nevertheless remains connected with its fellows by fine blue fibrils. Local isolation ceases at the first anastomosis, where two cytoplasmic cylinders unite in a single fiber within a single tubular collagenous sheath. Since collagenous partitioning always follows cytoplasmic partitioning it is always more advanced, more precocious around the cellular prolongations than around the nuclei. It appears last between the nuclei of the same isogenic group.

All of these phenomena begin and proceed in the degenerated fiber, even when it still contains fatty ovoids (Figs. 2, 4 and 8). They are seen even alongside of the ovoids themselves (Fig. 2), the presence of which does not interrupt the continuity of the schwannian syncytium.

In this way the schwannian syncytium of each degenerated fiber is converted into a retiform bundle exactly like an innervated bundle of regeneration before myelinization. This is not exactly what Nageotte observed. In his experimental material the col-

lagenous partitioning was roughly sketched but it remained incomplete, never advancing to complete cleavage. Nageotte held that complete cleavage is peculiar to innervated bundles and that it was determined by the intrusion of the neurites. My own observations show that the influence of the neurite is not indispensable. This is of capital importance for the understanding of neurinomas.

The collagen which forms in the place of, and without doubt at the expense of, the schwannian membranous septa without the intervention of any mesodermal cell, is an endoneurium — a neo-endoneurium — the endoneurium of an aneuritic bundle. It is exactly like the neo-endoneurium of an innervated bundle of regeneration. Like the latter it is invaded secondarily and occupied by typical endoneurial cells, but these cells have not created it.

Evolution of the Old Endoneurium
The Neo-Endoneurium

As I have already said, all of the phenomena just described begin inside of the original, thickened Plenk-Laidlaw sheath. This disappears as a sheath in a remarkable manner. In regions where the degenerated and hypertrophied fibers have not yet undergone collagenous cleavage (Figs. 1 and 11), each of them still enclosed in its collagenous sheath is surrounded by a sort of casing of gelatinous appearance, composed of an extremely delicate network, the fibers of which are non-argyrophil and stain but faintly with aniline blue. This casing encloses not only the collagenous sheath of the degenerated fiber but also a group of interstitial endoneurial fibers. These latter, which appear to be voluminous and deeply stained under low magnification, consist of numerous fibrils associated in bundles. The contours of the bundles are indistinct. They seem to dissolve into the gelatinous substance. A little reflection will show that this apparent jellification of the fibers is inadmissible. If they had swollen before disappearing, their colorability and their number would have diminished. On the contrary, their number has increased and their colorability is intensified. There is rather the impression that new fibers are forming little by little around the preexisting endoneurial fibers by condensation of the gelatinous substance which bathes them. The new fibers join the old ones to form the bundles. That which tends to confirm this idea is that as one approaches the cut end of the nerve the gelatinous substance de-

creases progressively and the collagen fibers, increased in number and deprived of their jelly, resume their habitual precision.

The gelatinous envelope surrounds each schwannian fiber exactly, constituting a sheath system. Between adjoining gelatinous sheaths there are clefts occupied by endoneurial cells and by a network of their branches. These cells have multiplied by amitosis. When the jelly has disappeared, these cells install themselves in its place between the liberated and multiplied fibers. Of the two types of cell present, the endoneurial cell and the schwannian syncytium, which seems to have the decisive influence on the production and on the increase of collagen? Everything favors the schwannian syncytium.

If we now examine attentively the Laidlaw sheaths which have become collagenized, we see that certain of them are reduplicated and that others are partially separated from the schwannian fiber, the cytoplasm of which is in contact with the gelatinous substance. This denudation of the syncytium lasts but a short time. A collagenous pellicle, consisting in reality of a delicate web of fibrils, especially circular fibrils, identical with the Plenk-Laidlaw sheath of the normal fiber, is being constructed and is replacing the initial cytoplasmic membrane. Thus the syncytium is soon enclosed in a new and very thin sheath which soon thickens in its turn (Fig. 11).

In brief, at the time when the old collagenous sheath is separating from the syncytium and becoming incorporated in the interstitial endoneurium, a new reticular sheath is being produced on the surface of the syncytium. The degenerated fiber seems to undergo a sort of moulting like that of the imago when it issues from the chrysalis. It is at this time that the internal collagenous septa begin to appear, those septa that convert the degenerated fiber into an aneuritic schwannian bundle. Thus the entire sheath system of the bundle of regeneration and even the interstitial framework of the endoneurium seem to be determined by the schwannian syncytium. Nageotte has said that the schwannian syncytium constructs the nerve and the neurites occupy it. We may add, I believe, that the schwannian syncytium constructs the endoneurial collagenous framework and the endoneurial cells occupy it.

The Infiltrating Schwannomas

Within the distal stump, as in the cut segment of the nerve, schwannian proliferation is moderate in degree (Figs. 5, 6, 7). Each

degenerated nerve fiber is transformed into an aneuritic bundle of regeneration broader than the primitive fiber which it has replaced. Usually at the end of three months the transformation is complete only near the cut ends. When the cut segment is very short, the change may involve the entire length of the degenerated fibers. However, in the original nerve the old fibers and the bundles derived from them do not elongate, neither do they form anastomoses.

At the ends of the cut segment there is a very different picture. From the cut surface there escapes a sheaf of aneuritic sprouts, continuations of the elements of the bundles of regeneration, which invade the surrounding connective tissue, anastomose with one another, reunite in bundles which in their turn soon ramify and join neighboring ramifications to form new bundles, and so on. Thus is constituted a peripheral fibroglioma of retiform or plexiform structure.

I shall dwell no longer on the general aspect of these schwannomas, which have been described so well by Nageotte, but only on certain features of their aneuritic fibers which alone interest us here. Some of the cellular bands which have long since invaded the connective tissue push no further. They are exactly like those of the incised segment. Cylindrical, enclosed in a thick sheath of collagen, they consist of a schwannian syncytium of elongated cells which do not fill the sheath completely. Between the cells and their processes there is more or less abundant fluid. Other bands are in active growth (Fig. 5); they consist of turgid cells that fill their very thin, reticular, collagenous sheath completely. Their nuclei are dividing, always amitotically. The isogenic groups of nuclei are being scattered rapidly by shifting and spacing of the nuclei along the fiber.

Beyond any doubt, the retiform structure is often constructed by lateral anastomosis of the advancing bands, as observed by Nageotte (Fig. 5); but it results also from longitudinal cytoplasmic partitioning followed by collagenous partitioning and then cleavage of the collagenous septa, exactly as I have described in the degenerated fibers which undergo hyperplasia in the incised segment. In other words, the invading bands are converted into aneuritic bundles (Fig. 6).

The isolated bands, the smaller and larger bundles, are always separated from the connective tissue by a more or less continuous layer of endotheliform cells, constituting miniature perineuria.

Around the smaller bundles there is a single layer; around the larger bundles they are stratified. Nageotte says that this newly formed perineurium is constructed by connective tissue cells from the invaded region which is adapting itself to its schwannian guest. For reasons which it will be more opportune to develop later, I have adopted a different opinion. For me, the endotheliform cells are cells which have emigrated from the endoneurium of the incised segments; they have followed the schwannian sprouts and construct protective sheaths for them.

I shall add a final observation. The perineurium of the degenerated nerve, delaminated, edematous, converted into a lacunar sheath, is invaded by many sprouts. These sprouts push into an optically empty fluid as free from albumin as is the cerebrospinal fluid. The sprouts are always enclosed in a reticular sheath reinforced by longitudinal collagen fibrils. Secondarily and later the endoneurial cells emigrate, and arrange themselves around the sprouts as miniature perineuria. I insist that the collagenous sheath of the sprout, the rudiment of its endoneurium, is constructed before any contact with an endoneurial cell, and under the sole influence of the schwannian syncytium (Fig. 7).

Summary of Part I

The schwannian syncytium enters on mitotic proliferation (Büngner) when the medullated axone which inhabits it has been separated from its trophic center and degenerates. The new nucleated territories conserve their syncytial relation. From the cut ends they invade the wound until the neurites, coming down from the proximal stump, penetrate them and together with them construct the bundles of regeneration.

If innervation is prevented, the proliferation of the schwannian syncytia continues both inside of the nerve and from the cut end. It becomes exuberant when the distal stump is cut a short distance below the first incision (Nageotte). The isolated piece of nerve gives rise to a voluminous, infiltrating, schwannian tumor.

Study of the syncytium in proliferation, both in the nerve trunks themselves and in the surrounding connective tissue, shows that each Schwann cell is capable of being transformed into an aneuritic bundle of regeneration, purely schwannian, retiform, and morphologically identical with the innervated bundles before their myelin-

ization. This transformation is accomplished (*a*) by repeated amitotic division, (*b*) by longitudinal cytoplasmic cleavage, and followed (*c*) by the production of tubular, ensheathing septa formed of reticular collagen.

The production of the ensheathing collagen and of the entire interstitial endoneurium of the bundle is determined by the schwannian syncytium. The rôle played by the endoneurial cells is distant and indiscernible. It is only after the endoneurial framework has been constructed that the endoneurial cells come to occupy it.

The schwannian bundles that invade the ordinary connective tissue are separated from it by an endotheliform perineurium, formed in all probability not by the common connective tissue cells of the neighborhood, but by cells emigrating from the endoneurium of the degenerated nerves and being transformed into endotheliform cells.

DESCRIPTION OF PLATES

PLATE 65

FIG. 1. Experiment I. Segment of nerve resected and left in place. Cross-section of middle. Trichrome stain with aniline blue.

The degenerated nerve fibers appear as pink circles mounted in blue (Plenk-Laidlaw sheath sclerosed). Their size varies greatly. Some (*a*) are scarcely broader than the largest fibers of the distal stump; others are four times as large (*b*).

All of the nerve fibers are divided into polygonal territories by septa dotted with dark red points (fibrils). Slight shrinking of some of the territories shows that in reality the septa are boundary membranes (membranes of Schwann). Some territories broader than the rest contain a nucleus. Some fibers present two nuclei (isogenic group) in the same transverse plane. In brief, each degenerated and secondarily hypertrophied fiber is converted into a schwannian bundle, composed of nucleated cell bodies and their multiple and anastomotic prolongations, all elongated in the direction of the nerve and crowded into the old Plenk-Laidlaw sheath (*b*), which has become collagenized. The fibers of this sheath, spread apart by the increase of the schwannian syncytium, are no longer contiguous as in the distal stump; they appear as blue dots.

Collagenous fibrils and then collagenous septa begin to replace the protoplasmic membranes of Schwann (*b'*). At (*b''*) the schwannian bundle, deprived locally of its sclerosed collagenous sheath, is enclosed in a thin collagenous pellicle of new formation and contemporaneous with the fibrils that begin to appear in the internal cytoplasmic septa.

Each degenerated fiber is enclosed in a thick, pale blue, gelatinous sheath which surrounds not only the Plenk-Laidlaw sheath, but also a group of collagenous fibers of the interstitial endoneurium (*e i*). Between the

gelatinous sheaths there are fissures occupied by proliferated endoneurial cells and by their anastomosing prolongations. In this jelly the collagenous fibers increase in number; those of the old Plenk-Laidlaw sheath exfoliate (*d*); then they separate little by little from the schwannian bundle and become incorporated in the interstitial endoneurium.

At (*b''*) the collagenous partitions isolate several schwannian prolongations from their fellows.

FIG. 2. Experiment I. Segment resected and left in place. Cross-section of hernia. Trichrome stain with aniline blue.

The magnification of this drawing is 2½ times less than that of Fig. 1. The aneuritic bundles of regeneration here represented are continuous with the degenerated fibers of Fig. 1, but they are two or three times broader.

Below and to the right (*a*) the collagenous partitioning of each schwannian bundle is less advanced than at the left, where it is complete (*b*) and at (*c*) where cleavage of the partitions is beginning. Three bundles still contain fatty ovoids (*d*).

(*e*) Bundles incompletely partitioned and cut almost longitudinally. The interstitial endoneurium is edematous but rich in collagen fibers. Some of them have belonged to the original Plenk-Laidlaw sheath; they have become collagenized and they have separated from the schwannian bundles. There is no longer a gelatinous casing around the bundles. Each bundle, together with its constituent elements, is surrounded by a new Plenk-Laidlaw sheath already thickened and collagenized.

(*f*) Split bundle, the elements of which begin to disperse.

(*g*) Epineurial connective tissue invaded by schwannian bands.

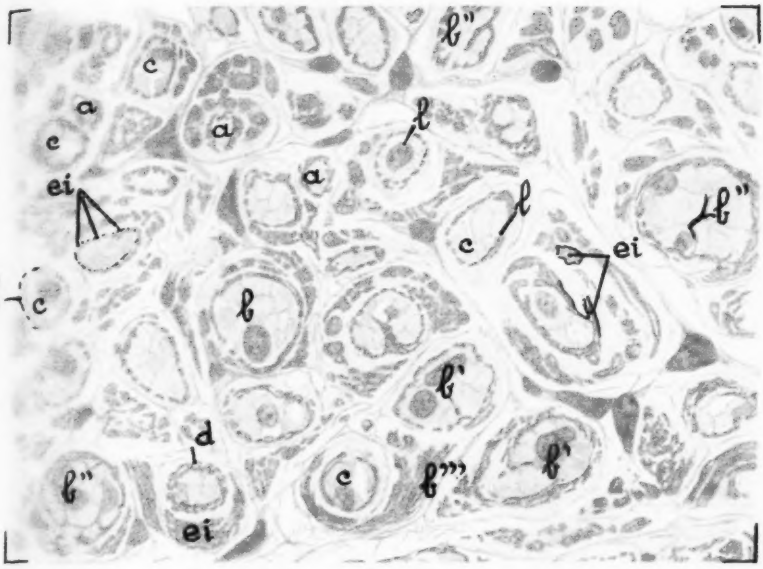
FIG. 3. Experiment I. Segment resected and left in place. Longitudinal section supposed to be from between the cross-sections represented in Figs. 1 and 2; this of course is from another block. The degenerated and slightly sinuous hypertrophied fibers are visible for only part of their length.

(*a*) The axis of this fiber is crowded with fat drops, residue of myelin. The margins of the syncytium are set with rows of nuclei. From one side to the other transverse anastomoses maintain the continuity of the syncytium in all directions. At the left the section, becoming tangential, shows the incomplete transverse separation of the nucleated territories and their elongation in the direction of the fiber. At the left are seen the longitudinal collagen fibers which surround the schwannian syncytium (new Plenk-Laidlaw sheath).

(*b*) On the right a striated appearance. The lighter bands correspond to the polygonal territories of Fig. 1; the darker lines correspond to the partitions seen in optical section and to their non-collagenized fibrils (*cf.* Fig. 1). On the left the same schwannian band; isolated in its substance is seen a delicate blue collagen fibril.

(*c*) Schwannian bands cut obliquely and distended by enormous fat drops. Delicate anastomoses connect the nucleated territories.

(*d*) Schwannian band cut in two places. On the right an isogenic group of nuclei beside a fat droplet. Immediately to their left collagenous partitions separate the prolongations of the cells; the partitions respect the anastomoses and ensheathe them. The crossed blue fibers are endoneurial collagen fibers placed above the schwannian bundle. On the left the same band presents a swelling containing a gigantic nucleus.



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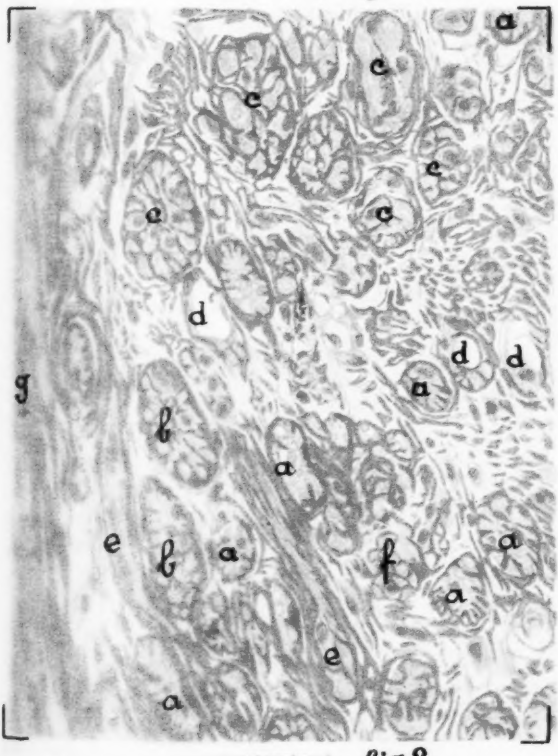


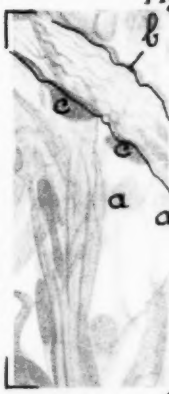
fig. 2

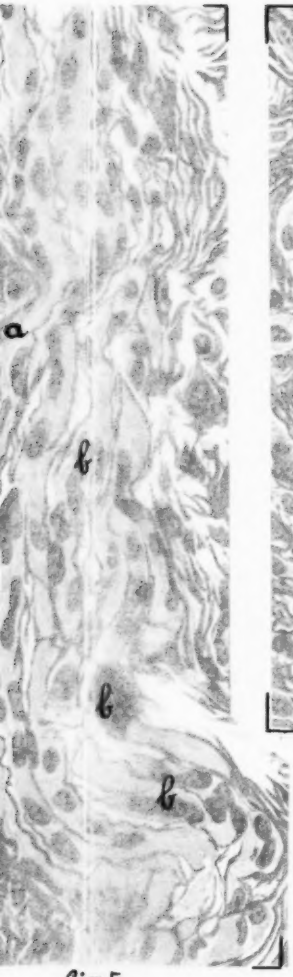
fig. 4

fig. 5

fig. 7

fig.4





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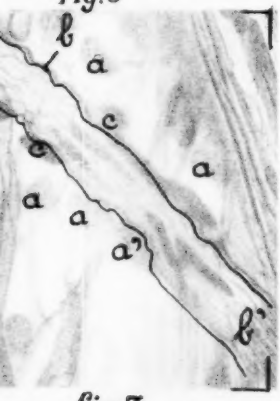

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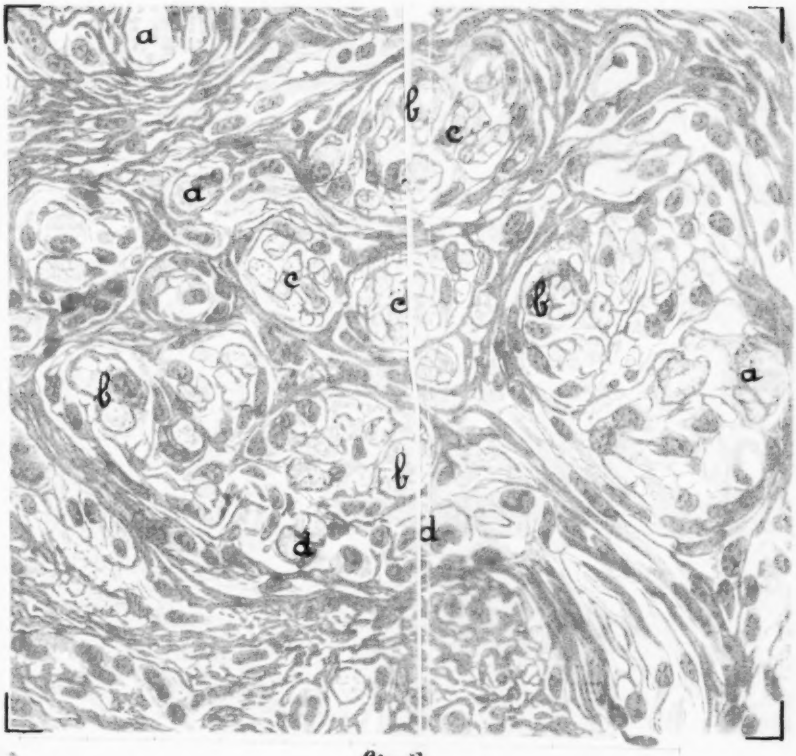

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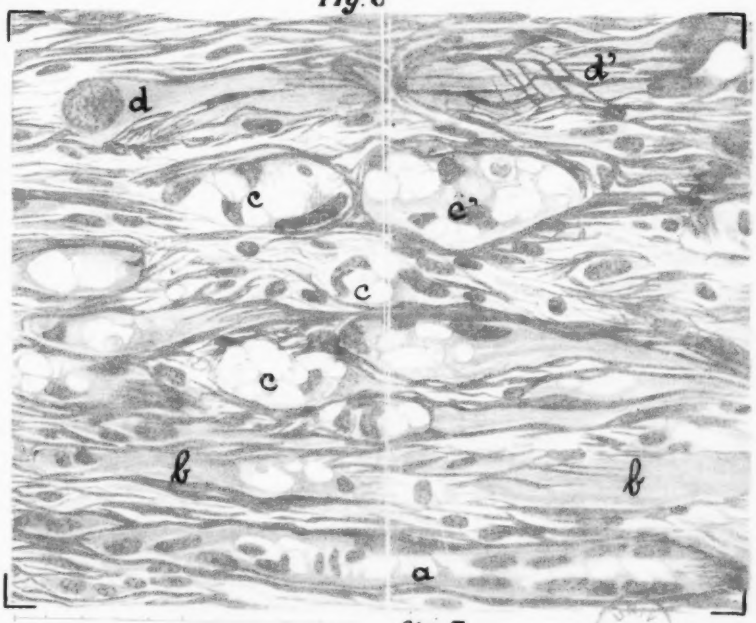
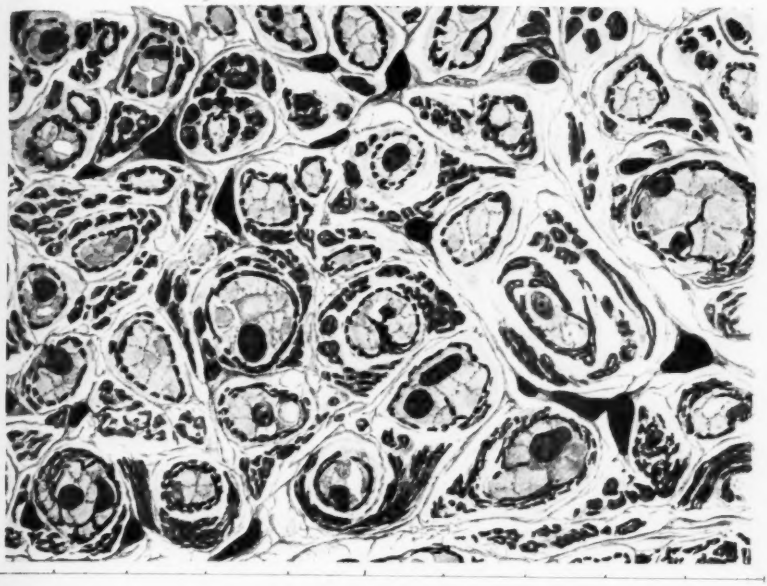


fig. 3



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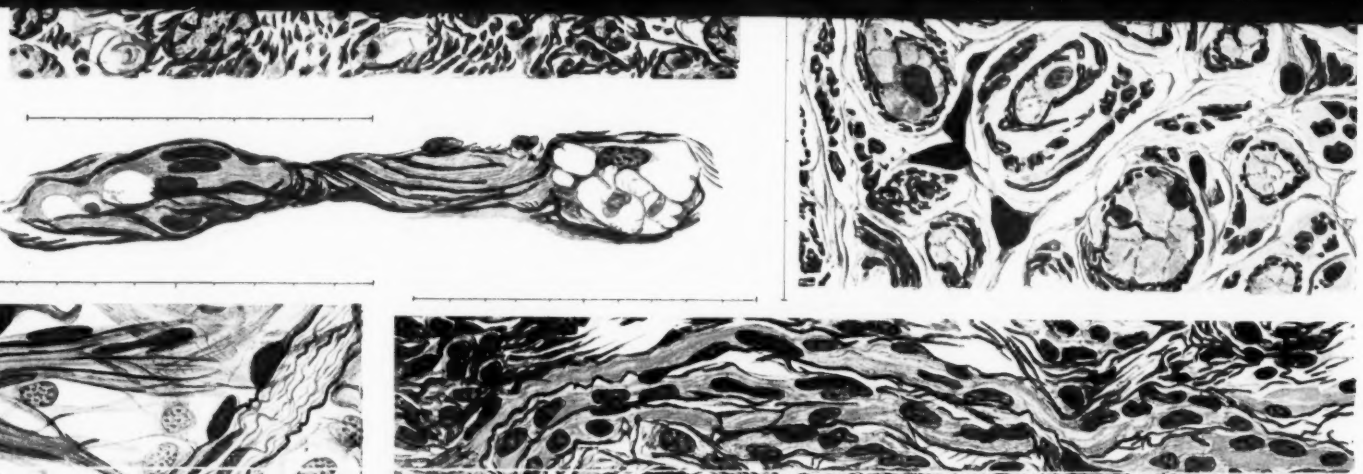

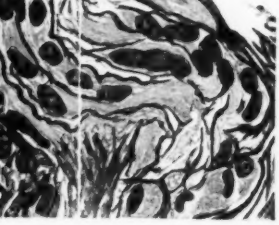

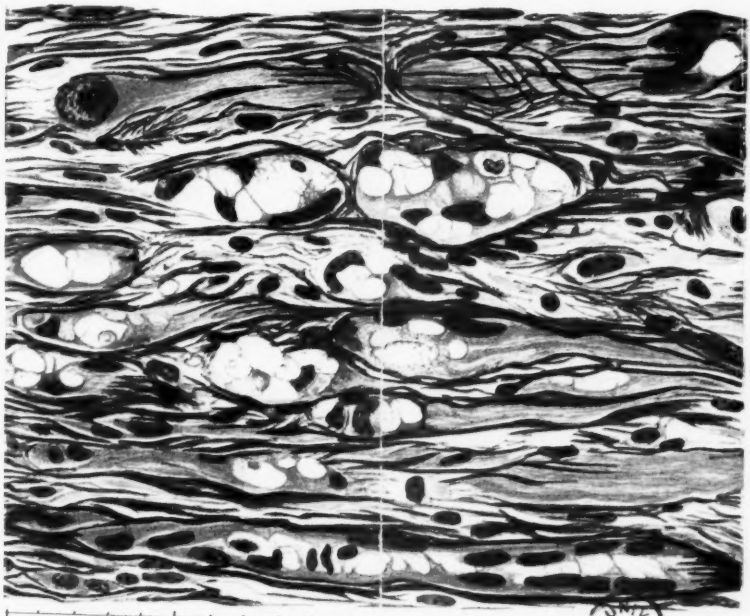

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Experimental and Spontaneous Schwannomas. I

FIG. 4. Segment resected and left in place. Same preparation as Fig. 3. A degenerated fiber converted into an aneuritic bundle between two fatty ovoids.

(*a*) Isogenic group of nuclei; on the left not yet separated by collagenous septa; on the right so separated.

(*b*) Cellular prolongations partially separated by septa which cease in region (*c*) where there is a large ovoid. The partitioning therefore is more precocious between the prolongations than between the nuclei.

(*d*) Collagen fibrils of the new Plenk-Laidlaw sheath.

(*e*) Remains of the gelatinous sheath.

FIG. 5. Experimental schwannoma. Experiment II. Young schwannian bands invading the connective tissue. Note their retiform arrangement. All of them are enclosed in a thin collagenous sheath which silver staining shows to be finely reticulated. At (*a*) the bands show distinct striation between the nuclei. The nuclei are dividing by amitosis. At (*b*) they form isogenic groups, rapidly dispersed owing to their shifting along the fiber which is elongating actively.

FIG. 6. Experimental schwannoma. Experiment II. Schwannoma invading the connective tissue. Bands older than those of Fig. 5.

This figure shows the stages of cleavage of the schwannian bands.

(*a*) Their transformation into bundles, at first protoplasmic.

(*b*) Their progressive collagenous partitioning. The collagen appears in the center of the band as well as along its borders where it has the appearance of spur-like processes.

(*c*) Cleavage of the collagenous septa followed by separation of the bands.

(*d*) Broadening of the bands.

The figure shows the progressive ensheathing of the bands and of the bundles by flattened cells which separate them from the connective tissue. These miniature perineuria spring perhaps from the regional connective tissue, adapting itself to the schwannian bands (Nageotte). However, I make every reservation in this interpretation. I believe that the new perineurium is formed of endoneurial cells of the incised nerve, which have followed the schwannian sprouts.

FIG. 7. Experiment I. Invasion of the edematous perineurium of the distal segment by a schwannian band.

The syncytium consists of very long cells with slender prolongations, highly retractile, bathed in a colorless fluid.

(*a*) Thin, pale perineurial cells. Cell (*a*) is not in contact with the schwannian band but on a lower level. The framework is surrounded by its reticular collagenous sheath (*b*), visible as a blue line bordering the band, or as a light blue veil at (*b'*) (tangential section).

(*c*) Mobile cells from the endoneurium which are beginning to lay down a perineurial sheath. This sheath is discontinuous and very recent. The collagenous sheath exists before the arrival of these cells. It is determined by the schwannian band.

PLATE 66

FIG. 8. Aneuritic bundle of regeneration from the margin of the endoneurial hernia (Experiment 1).

Below, swelling of the old schwannian band containing fat droplets. The bundle has escaped from the nerve. Its collagenous cleavage is finished and the young sprouts invade the surrounding connective tissue, assuming successively the aspects of Figs. 5 and 6.

FIG. 9. Another bundle near that of Fig. 8.

In the lower half note the group of isogenic nuclei that have remained in the same transverse plane and form a palisade. The nuclei are flanked above and below by a collagenous fibrillar layer, very dense, composed of the collagenous sheaths which enclose each of the cellular prolongations above and below. They constitute a collagenous palisade on each side of the nuclear palisade.

In the middle, a schwannian band of the same bundle, in process of elongation, shows four isogenic nuclei which have ranged themselves in a row. On the right and left, other bundles are cut obliquely.

FIG. 10. Experiment I. Graft of sciatic nerve near the end. Images similar to those of Figs. 1 and 2. The endoneurial edema is much less pronounced. The degenerated fibers show all the stages of longitudinal cleavage and collagenous partitioning.

FIG 11. Experiment I. Segment resected and left in place. Middle region.

Two regenerated and hypertrophied fibers, freed from their old collagenous sheath, show in places their newly formed Plenk-Laidlaw sheath, either as delicate circular fibrils (curve of the central fiber) in tangential sections, or as dots in longitudinal sections (central fiber and fiber to the left and above).

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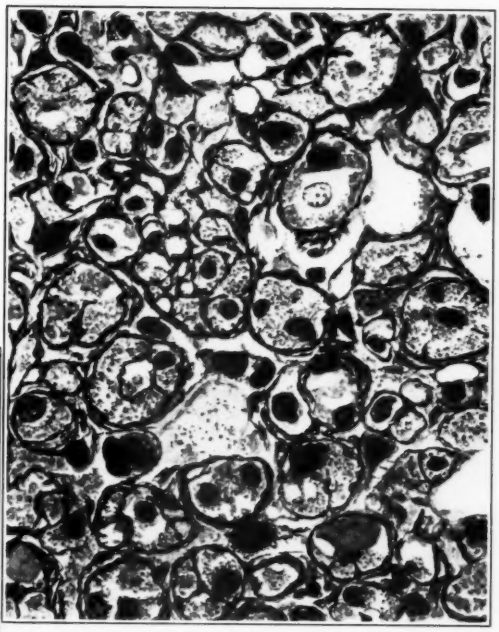

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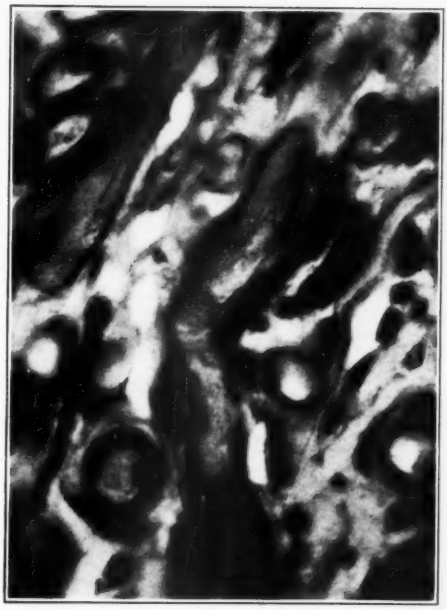

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Experimental and Spontaneous Schwannomas. I

EXPERIMENTAL AND SPONTANEOUS SCHWANNOMAS (PERIPHERAL GLIOMAS)*

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PART II

SPONTANEOUS SCHWANNOMAS

INTRODUCTION

The tumors to be discussed here are the encapsulated tumors of the peripheral nerves (neurinoma, lemmoma, peripheral glioma, neurofibroma and perineurial fibroblastoma) situated outside of the cranial cavity and outside of the spinal canal. I shall not touch on the encapsulated tumors of the cranial nerves or on those of the spinal nerve roots, not because these tumors are without interest or any different from the others, but simply because circumstances have not permitted me to accumulate a sufficient number of examples.

I shall take no account of the number of tumors in the same subject. The distinction between solitary and multiple tumors is purely clinical; it has no scientific value. A diagnosis of solitary tumor would have to be controlled by dissection of every nerve in the body; an accessible voluminous tumor may seem to be solitary, while others, smaller and situated more deeply, escape palpation. Furthermore I believe that solitary and multiple tumors are identical in structure.

THE CAPSULE

The characteristic element of these tumors, the capsule, enables us to eliminate from the discussion other tumors of the same nature, but infiltrating and diffuse. The capsule, formed of lamellae, envelops the tumor except at the point of attachment of the nerve. Here it is continuous with the perineurium and it probably represents the former perineurium distended locally by the growth of the tumor within it. This feature is important for it shows that the tumor is composed of one or several of the elements of the normal nerve enclosed within the perineurium.

* Received for publication March 18, 1932.

The Tumor Tissue. Classic Data

Among neurinomas, Antoni distinguished two structural types, Type A, fasciculated and clearly polarized, that is, arranged in elongated bands, and Type B, reticular, without polarity. Type A often presents palisading, the description of which is usually ascribed to Verocay; but it was noted before Verocay by von Hippel, Mayer, Francini, Antoni and others. The palisading is inconstant but absolutely pathognomonic when present. Type B, the reticular type, is constant. Probably it arises by dedifferentiation of Type A. It is characterized by hyaline degeneration of the intercellular substance. In short, despite its three possible aspects, fasciculated, palisaded and reticular, the neurinomatous tissue is a unity. The palisading is a complication of the bundles; the reticular is a degenerated form.

The basic substance is composed of delicate reticulated fibrils staining blue with Mallory's connective tissue stain (aniline blue), yellow or orange with Van Gieson's and black with Bielschowsky's method. When degenerated they become transparent like hyaline substance but softer, more like jelly. Neurofibrillar impregnation methods sometimes reveal a few neurites. It is improbable that these neurites form an integral part of the tumor; they are old neurites of the nerve trunk in which the tumor has grown.

This classification of the structural aspects of neurinomas seems to me to be very judicious. Like many of my predecessors I adopt it, not *a priori* but *a posteriori*, because my observations lead me to believe that it includes the essential facts; but the description of each tissue type, as one may read it in Antoni, is much too succinct. The same may be said of the innumerable subsequent descriptions. Each of them has brought to the support of the schwannian hypothesis of neurinomas a fresh confirmation of the structures seen by Antoni or some new structural details; but no one of them has assembled a group of arguments sufficiently convincing to rout the partisans of the fibroblastic hypothesis.

Technique

It seems to me that this shortcoming is due to the universal use of the same techniques, first and foremost Van Gieson's. I shall not speak of the hematoxylin and eosin stain which should long ago

have been relegated to a museum of antiquities. Many who have used Mallory's methods and silver impregnations of collagen would have seen decisive things, if instead of using these techniques separately they had used both of them on the same section. In my own studies I have used the trichromes, derived from Mallory's aniline blue method, either alone or combined with Laidlaw's silver stain for reticulin, after fixation in Bouin's picro-formol.

Basic Material

My studies were greatly facilitated by one specimen, a circumscribed painful tumor that elevated the mucosa of the anterior region of the palate in a girl 17 years of age. In the course of several months this tumor had attained the size of a bean. Finally the mucosa over the tumor ulcerated and the tumor grew rapidly. Examination of a biopsy removed by Dr. Ph. Panneton of Montreal revealed a typical neurinoma with many bundles and beautiful palisading. Eight days later the tumor was extirpated and it has not recurred.

The biopsy had the peculiarity that, having been recently and superficially infected, it was infiltrated by an abundant edema which dissociated the elements of the neurinoma before they had time to degenerate appreciably. The tumor itself was still more edematous. Many of its cells had disappeared, permitting an easy study of the collagenous framework. The edema being recent, especially in the biopsy, and occurring in a neurinoma of rapid growth, it permitted an examination of the bundles and of the palisades in exceptionally favorable circumstances. Later I was able to discover the same features in all of the neurinomas examined.

Every neurinoma grows; its constituents multiply, enlarge and evolve. In order to understand them they must be studied not only as functions of three dimensions in space, but as a function of time. Obviously this latter factor will escape micrographic technique, but one can, I believe, deduce it from the histological aspects and introduce it into the argument with small chance of error. We shall study successively the essential elements, the bundles and the palisades (Type A); then the degenerated forms, that is to say, the sclerosis attributed to the intrusion of connective tissue, and finally the reticulated areas (Type B).

I. THE BUNDLES

The basic element of the bundle — the nucleated ribbon, the syncytial band — is in reality a nucleated cytoplasmic joist of circular cross-section. It is a cylinder, but a cylinder unequally calibrated and without free ends, being continuous with other cylinders. The cylinders are not only continuous longitudinally but they are also united laterally by oblique cylindrical anastomoses. Connected thus in all directions they form a net-like assemblage of three dimensions, the meshes being drawn out along the length of the fiber. The meshes are so elongated that the constituent cylinders are nearly parallel and so close to one another that they leave only long, narrow chinks, often mere potential spaces, between their surfaces of contact (Diagram 1).

The Cylinders

Accurate cross-sections of a compact bundle show that the caliber of the cylinders is quite variable and that their structure is not less so. In general the caliber and the structural complication are proportionate (Fig. 3). By separating them the edema * makes their study easy in serial sections and permits of facile reconstructions (Figs. 1 and 2).

A Simple Cylinder

First of all I shall describe an elementary cylinder, as simple a one as possible, disregarding its connections. As a center I shall assign it a nucleus and for ends an imaginary transverse plane cutting it on either side of the nucleus halfway to the next nuclei of the same cylinder (Fig. 2 (*g*)).

(*A*) *Trichrome Blue:* (Fig. 2). The cylinder is not geometrically perfect. At the level of the nucleus it is enlarged, its diameter being about 7 microns, whereas near the ends, especially if it is very long (30 to 40 microns), it measures barely 2 to 3 microns in diameter. Its cytoplasm is colored uniformly deep pink. The nucleus does not fill nearly the entire area of the cell as happens in spindle-cell sarcoma, but only one-third or one-fourth. The form of the nucleus

* I refer to a true edema, a recent acute edema such as I have observed in my neurinoma of the palate, and not the false edema characteristic of Antoni's Type B. The former reveals but leaves intact the structures that I am about to describe; the latter results from their slow degenerative destruction. It is not in Type B, therefore, that these structures should be sought.

is a long oval, often irregular, broader at one end than the other. Often it is fissured. Its scanty chromatin is arranged in a delicate marginal net. In the nuclear juice there are always one or more perfectly round and basophilic nucleoli. The nucleolus may be turgid and hollowed out by a large colorless vesicle which distends it.

The cylinder is never naked. It is always enclosed in a thin envelope staining blue with this technique and moulded exactly on the cylinder. In this sheath there may be distinguished very fine fibrils of nearly circular course and others a little more voluminous of longitudinal direction.

(*B*) *Van Gieson:* Using the powerful acid fuchsin of the National Aniline Co., of New York, the longitudinal fibrils show very well but not the circular ones. In cross-sections the protoplasmic cylinder seems to be stippled in red (cross-sections of longitudinal fibrils), the dots being united by a thin orange line.

(*C*) *Laidlaw's Silver Technique Followed by Ponceau-Acid Fuchsin and Light Green:* This gives important additional information (Fig. 3). The cytoplasm of the cylinder no longer has the homogeneous appearance described after trichrome staining (probably the mordanting action of the potassium permanganate). Its colorability by ponceau has partly disappeared. The only reds are the delicate lines which in cross-sections divide the cytoplasmic area into tiny polygonal territories and which in longitudinal sections trace a delicate striation. By changing the focus it is seen that the septa and the longitudinal markings are one and the same thing; they correspond to tubular septa which divide the initial cytoplasmic cylinder into many smaller cylinders incompletely separated from one another. At the ends of an elementary cylinder the partitioning is more or less perfect. In the nuclear swelling it is absent or imperfect; if present it is along the margin only.

In cross-sections the sheath enclosing the cylinder appears in general as a narrow green border dotted in black. Longitudinal sections show that the black dots correspond to cross-sections of the longitudinal fibrils just described as stained by aniline blue and picro-fuchsin. Exceptionally the silver impregnates a delicate web of reticulin (Fig. 11) visible in certain tangential sections, and it occupies exactly the place of the green sheath.

The resemblance of this web to the Plenk-Laidlaw endoneurial sheath is striking. We may ask whether it exists only around those

cylinders where it is visible or around all of them. As well put the same question for the normal nerve fibers where the visibility of the Plenk-Laidlaw web is far from constant and depends largely on the fixative employed. Picro-formol, which I have used in these observations, is less favorable for its exhibition than the Zenker fixation recommended by Laidlaw. In these picro-formol sections, then, there is no reason for surprise at the exceptional and merely local success of silver impregnation of the web which probably exists around each cylinder. Even when the web is impregnated, it does not seem to be a net with empty meshes; the meshes seem to be occupied by a thin pellicle staining by the light green or by the aniline blue.

Relations of the Elementary Cylinder to the Interstitial Tissue

This sheath is remarkably adherent to the cylinder. The interstitial edema never separates them but the edema shows that, through its longitudinal fibrils, the sheath is continuous with the other longitudinal argyrophil and collagenous fibrils. These latter fibrils are more voluminous, brush-like, anastomosing, and situated in the interstices between the cylinders just as the fibrils of the interstitial endoneurium are situated between the medullated fibers of a nerve (Fig. 8). The analogy between these fibrils and those of the endoneurium is completed by the presence in their interstices of a few branching cells with filiform processes and spongy cytoplasm. These cells are absolutely naked; they have no collagenous or reticular sheath. A few argyrophil fibers run alongside of them but there is lacking that intimate relation which binds cylinder and sheath. This is true not only of the simple cylinders just described but also of the others. It is unnecessary to repeat the description.

More Complex Cylinders

The caliber of these cylinders is still more variable than of those just described, being from 3 to 10 microns at the ends and from 7 to 50 or 60 microns at the nucleus.

(*A*) *Trichrome Blue:* (Figs. 1 and 2). The cytoplasm has the same features as in the simple cylinders. The nuclei are often fissured longitudinally or split into two or three. They may remain in the same transverse plane (Figs. 2 and 3, broad cylinders) or they

may separate, shift their position and range themselves in longitudinal rows (Fig. 4). Thus there is amitotic multiplication of the nuclei (in the many neurinomas studied, I have seen only one mitosis) with production of isogenic groups. When the group of nuclei remains in the same transverse plane, the cytoplasm of the cylinder broadens at this point; when the nuclei range themselves longitudinally, the cylinder elongates but remains narrow.

In cross-sections it is seen that the blue collagenous sheath still fits the cylinder closely, but it presents internal spur-like projections, simple at first, then branching, finally uniting with one another in a more or less continuous network. Here and there are points where blue septa appear in the heart of the cytoplasm with no apparent relation to those of the periphery, but soon making connections with them. Longitudinal sections show that these spurs are cross-sections of longitudinal septa and that the resulting network corresponds in reality to a cross-section of the longitudinal collagenous septa which cuts the cytoplasm of each primitive cylinder into smaller cylinders. They are tubular septa like those which enclose the primitive cylinder; but they are incomplete and spare the transverse connections of the initial cytoplasm.

The partitioning is always much more advanced at a distance from the nuclei than beside them. It is always followed sooner or later by cleavage of the collagenous septa and consequent separation into secondary cylinders. When the cleavage is precocious the cylinders are small; when it is late the primitive cylinders may acquire an enormous diameter before splitting (Fig. 3). It is conceivable that the predominance of small or of gigantic cylinders in such or such a neurinoma may give to these tumors quite different aspects without there being any essential difference in their structure.

(*B*) *Van Gieson:* This stain colors the spurs pale pink, the longitudinal fibers bright red.

(*C*) *Silver-Ponceau-Light Green:* This technique shows that the collagenous spurs and septa replace the cytoplasmic septa exactly (Fig. 3). Usually the longitudinal argyrophil fibers make their appearance in the amorphous collagenous septa (I have never succeeded in impregnating a web of circular fibers); less often they appear in the still cytoplasmic septa of the cylinders (Fig. 3 (*b*)). It is obvious that between the simple cylinder and the complex

cylinder there is no essential difference except the degree of their complexity, and everything goes to show that this complexity is progressive — that it corresponds to evolutionary stages of the cylinders.

To recapitulate, the cylinder undergoes longitudinal partitioning, carried out first of all by tubular cytoplasmic membranes; it is completed first at a distance from the nuclei, finally reaching the nucleated zones. Later there occurs collagenization of these septa, then cleavage of the collagenous septa followed by their partial separation. Between the newly formed cylinders some of the longitudinal argyrophil fibers are liberated, forming a delicate framework identical in every respect with the neo-endoneurium of a bundle of regeneration, whether innervated or not. This framework may be occupied secondarily by branching cells of endoneurial type; but the framework is not made by them any more than the framework of the bundle of regeneration is made by the endoneurial cells. It is the cylinder alone that determines the production of the framework.

In brief, the evolution of the elementary cylinder of a neurinoma is not only similar to but identical with that of the Schwann cell when, deprived of its neurite, it becomes an aneuritic bundle of regeneration. The sole difference consists in this, that in the neurinomatous cylinder the partitioning may be pushed further, dividing the cytoplasmic cylinder into a greater number of secondary cylinders, especially at a distance from the nuclei. In this event, each cylinder is extremely thin (barely 1 micron) but it is still enclosed in its argyrophobe sheath of collagen containing argyrophil fibrils.

Constitution of the Bundles

Having become familiar with the structure and evolution of an elementary cylinder, it is easy to understand how the bundles are constructed (Diagram 1). If the nuclei, the product of amitotic division, separate immediately from one another and range themselves along the length of the cylinder, the result will be a simple cylinder growing longer and longer. Between the widely separated nuclei, the longitudinal and incomplete partitioning of the cytoplasm and collagenization of the septa will convert the primitive cylinder into a linear, retiform syncytium similar to that which is produced in three months at the expense of and in the place of the

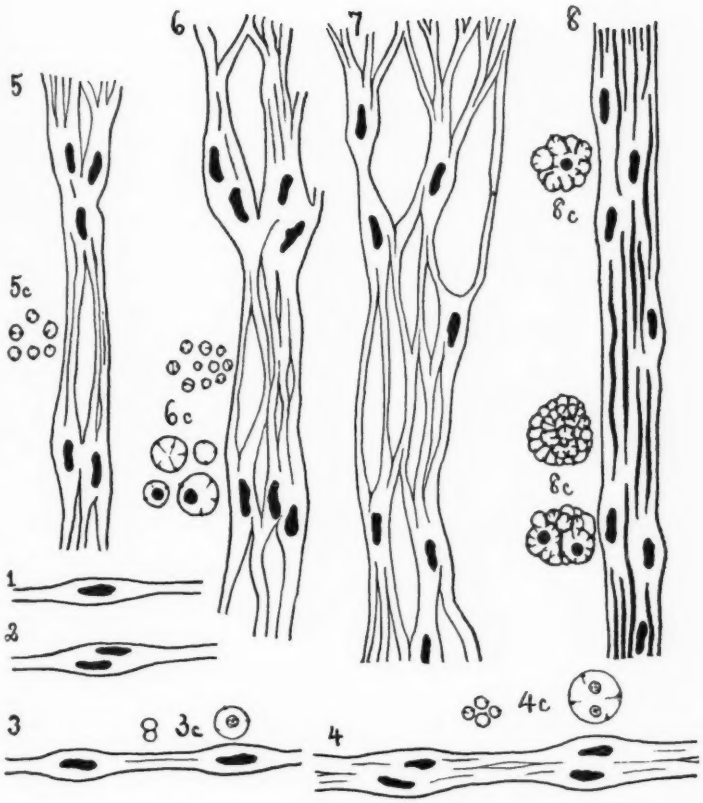

DIAGRAM 1

Neurinoma. Evolution of a simple cylinder; its transformation into a bundle. (4 to 7) The bundle in process of formation is dissociated by the edema.
(8) Aspect of bundle (7) not dissociated by edema.
(3*c*), (4*c*), (5*c*), (6*c*) and (8*c*) Represent cross-sections of the bundles bearing the same numbers.

degenerated medullated nerve fiber in the incised segment of a nerve in which regeneration has been prevented (see Part I).

However, as we have already noted, even in the experimental aneuritic bundle, there is very pronounced broadening in the region where its evolution is furthest advanced (the hernia). This broadening is always characterized by the presence of several nuclei in the same transverse plane. Conversely the active elongation observed in the zone of invasion is always characterized by shifting of the isogenic nuclei along the fiber. The nuclei are never placed one behind the other in a straight line parallel with the axis of the cylinder. This is due to the fact that in an isogenic group each nucleus occupies a different sector of the cylinder. When a nucleus, together with its cytoplasm, shifts along the lengthening cylinder, it remains for a time in the prolongation of the sector in which it first appeared; hence the irregular line of the shifted nuclei seen in longitudinal section.

In the bundles of the neurinoma, the nuclei behave similarly. Sometimes they are ranged in series along a cylinder (Fig. 4); sometimes they remain in the same transverse plane or nearly so. Under these conditions, when the partitioning and the subsequent collagenous cleavage reach the region occupied by an isogenic group of nuclei that have remained transverse, each nucleus becomes separated from its neighbor; but here, as in the internuclear zone, the separation is never complete. Always there persist transverse and sheathed cytoplasmic anastomoses which maintain the transverse symplastic continuity of the nucleated enlargements here as everywhere else (Figs. 1, 2 and 3 (*d*)). Secondarily these transverse anastomoses become slanting, due to unequal shifting of the nucleated enlargements, a shifting induced by unequal elongation of the bundles. From this time forward the anastomoses tend to run in a longitudinal direction like the bundles themselves.

We may suppose that in each bundle the retiform structure of three dimensions perpetuates itself indefinitely, owing to the alternating but capricious interplay of amitosis, followed sometimes by rapid longitudinal shifting of the nuclei, sometimes by precocious partitioning of the isogenic groups of nuclei that have remained transverse. Precocious longitudinal shifting of the nuclei and of their cytoplasm lengthens the cylinders and the bundles; precocious par-

titioning of the isogenic groups of nuclei multiples the cylinders and broadens the bundles.

In conclusion, from all points of view the elementary structure and the evolution of the fasciculated cylinders of neurinoma are similar to those of the schwannian bands in a nerve that has been sectioned but not innervated. In both situations the endoneurial cells are present during the changes in the bands and in the cylinders; but they themselves do not undergo any changes. The fundamental element of neurinoma therefore is the schwannian syncytium and not the endoneurial cell.

II. THE PALISADES

Classic Data: As observed in routine stains, the palisades consist of oval nuclei aligned in the same transverse plane "like staves of a barrel" (Verocay). On each side of this nuclear palisade, or on one side only, there is a fibrillar band parallel to it. The fibrils are oriented like the nuclei, running perpendicular to the nuclear band. With Van Gieson's solution they stain yellow or pink, sometimes red. With the silver method they impregnate like reticulin. When the sections happen to show the full length of the fibrils, it is seen that the fibrillar band is really stretched between two parallel nuclear palisades. It seems to unite them, forming a fibrillar palisade between two nuclear palisades.

Thus a "palisade system" is formed by two nuclear palisades parallel with each other and an intervening fibrillar palisade. Such simple palisade systems are frequent in neurinomas, but still more frequently the palisades present a more complex structure. Instead of being straight they may curve in more or less intricate ways. Several systems of palisades may be superposed to form an alternating series of nuclear and fibrillar bands parallel with one another; or the superposed nuclear palisades may appear in the sections as broken lines, sawteeth, anastomosing at their angles. In this way the nuclear bands describe a sort of net with lozenge-shaped meshes, the spaces being filled by the fibrillar palisades.

At some point these palisade systems are always attached to the bundles or to their reticulated, degenerated forms as seen in Type B. When complex, the palisade systems may attain considerable size, forming clearly circumscribed nodules which push the surrounding

tumor tissue before them and compress it. These palisaded nodules may be so voluminous or so numerous and confluent that they themselves constitute almost the entire tumor, the bundles being reduced to the position of occasional elements. The palisaded nodules differ from the bundles not only by their general aspect but also by their more rapid and independent growth.

Personal Observations: Francini showed long ago that in their structure the palisades do not differ essentially from the bundles. The techniques employed by me confirm this view.

Rudiments of Palisades

On examining certain cylinders of bundles that are distinctly polarized but which have been dissociated by edema, there is often seen between two consecutive nuclei a transverse blue band that is striated longitudinally. This band consists of the many collagen sheaths that surround each of the tiny cytoplasmic cylinders resulting from very advanced cleavage of the primitive cylinder. Here the collagen is more abundant because there are more sheaths in close contiguity (Figs. 4 and 8). In bundles that are not so dissociated, several similar blue bands may be found on almost the same plane; by their juxtaposition they describe more or less straight palisades of collagen.

Elementary Palisade Systems

(*A*) *Trichrome Stain:* Serial sections of a palisade system made at a right angle to the long axis of the nuclei and to the direction of the fibrils appear as follows:

In sections passing through a nuclear plane, the almost round nuclei are set close together in a common cytoplasmic mass; the cytoplasm is partially divided by incomplete collagenous septa. Many of the nuclei are fissured or they may form small groups (isogenic groups) enclosed in the same cytoplasmic body.

In sections passing through the ends of a nuclear plane (Fig. 9), a few nuclei are still seen but the collagenous septa separate them more completely than at the level just described. Alongside of the nucleated areas there are others free from nuclei, of the same caliber or smaller, in process of longitudinal cleavage.

In sections passing through a fibrillar plane, if the palisade is compact it appears to be formed of many pink dots in an undivided blue mass. Obviously each pink dot corresponds to the cross-section of a slender protoplasmic prolongation from the nucleated areas. Among them are found oblique sections also.

Following the series of sections, the same aspects appear in reverse order. The pink dots, representing the cytoplasmic prolongations, diminish in number, grow larger; then the nuclei embedded in their incompletely partitioned cytoplasm reappear.

When edema infiltrates a fibrillary palisade, it isolates each cellular prolongation from its neighbors and shows not only that each prolongation is provided with its own tubular sheath but also that each sheath is split off, separated from its neighbors and individualized. Between these collagenous tubes there are a variable number of collagen fibers running in the same direction (Fig. 10).

Thus each nuclear palisade is connected with its neighbor by a series of protoplasmic prolongations sheathed with collagen. Most of them connect the nucleated territory of one palisade with another exactly opposite to it in another palisade. Others run obliquely, uniting two adjoining prolongations or two nuclei not situated opposite each other. Obviously in the heart of the palisade system, there is a repetition of the retiform arrangement of three dimensions that we have described in the bundles. Examination of longitudinal sections confirms this view precisely (Figs. 5 and 6).

(*B*) *Laidlaw-Ponceau-Acid Fuchsin-Light Green Stain:* This technique reveals here too the presence of fibrils either embedded in the septa and sheaths or free in their interstices (Fig. 7). Scanty in the incomplete septa of the nucleated palisades, they expand abruptly in a sort of brush at the margin of the nucleated palisade; here they are distributed among the sheaths which enclose each cellular prolongation, from three to five fibrils to each sheath. These fibrils come together again close to the next nucleated palisade, but their point of reassembling is seldom opposite their point of departure (Figs. 7 and 19).

Thus the palisades offer three colors: pink dots (cross-sections) or pink lines (longitudinal sections) connecting the cytoplasms of two nucleated palisades, argyrophil dots or spindles, and in the interstices of these linear structures a diffuse green, corresponding to the ensemble of collagenous sheaths which surround each cytoplasmic prolongation.

In this description I trust that I have shown that in neurinomas the palisades have the same essential structural features as the polarized bundles. Therefore if the structural identity of the polarized bundle with the aneuritic schwannian bundle of regeneration leads us to consider the polarized bundles as of schwannian and not of connective tissue origin, we have every reason to believe that the palisade systems are schwannian also.

The Schwannian Palisades are Pathognomonic of Schwannomas

Since the time of Francini, Verocay and Antoni, palisading has been accepted as pathognomonic of neurinomas. The partisans of the mesodermal hypothesis of these tumors oppose to this idea: (1) the palisade arrangement of the muscle fibers of the obliterated appendix first observed by Oberndorfer; (2) similar fibers in the stomach and intestine; (3) the palisades that are indisputably seen in certain leiomyomas; (4) and here I shall make every reservation,* in certain fibromas and spindle-cell sarcomas.

Let us say at once that the palisades which correspond either to a "state of repose" (appendix) or to a state of contraction (stomach and intestine) of the muscle fibers, or to "rhythmic disposition of the muscle cells" (Lauche, Krumbein), have none of the specific structural features of the schwannian palisades as I have just described them. There is lacking the ensheathing of the anastomotic prolongations stretched between two nucleated palisades by homogeneous collagenous sheaths containing argyrophil fibrils. It is conceded that neurinomas are not the only tumors possessing palisades; but to be pathognomonic of neurinoma the elements of the palisade must have the specific structure of the schwannian elements. Nestmann has expressed the same idea in another form.

Significance of the Palisades in Schwannomas

We must now put to ourselves the question — what is the significance of these schwannian palisades? There is one consideration which dominates the problem first of all: certain neurinomas have no palisades. Nevertheless, in all of them the polarized bundles have the same structure.

* The palisaded "connective tissue tumors" invoked as arguments against the schwannian hypothesis are precisely these encapsulated tumors of the nerves.

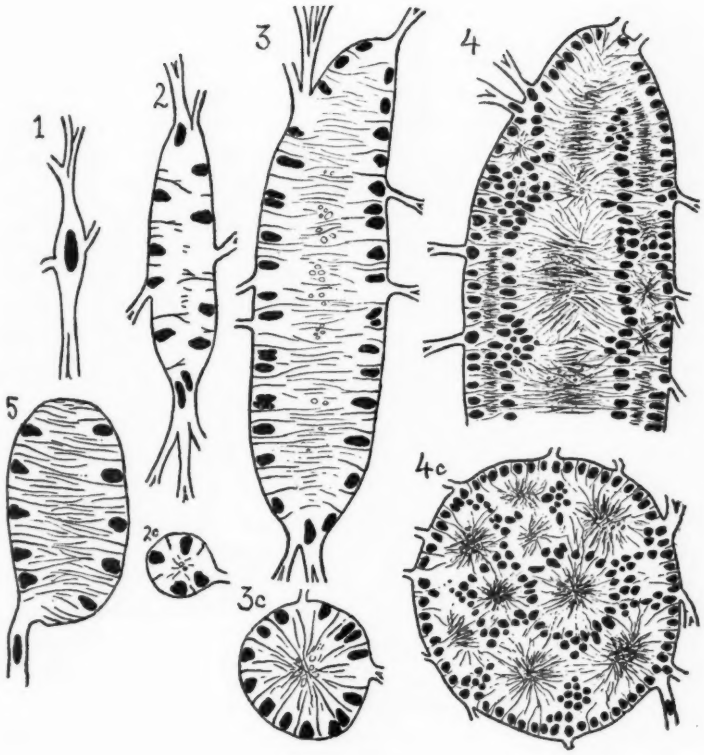

DIAGRAM 2

Neurinoma. Histogenesis of a palisaded nodule.

(1) Simple cylinder.

(2) Elongated and broadened cylinder; its nuclei marginal. Transverse septa are appearing (*cf.* Fig. 13).

(3) Continuation of the broadening, elongation and transverse partitioning. In this stage the meissnerian structure is typical (*cf.* Figs. 14, 15, 16). Between the marginal nuclei the striation of the collagenous palisades becomes accentuated.

(2*c*), (3*c*) and (4*c*) represent cross-sections of (2), (3) and (4).

(4) Appearance of new nucleated and collagenous palisades and production of a complex palisaded nodule (*cf.* Figs. 17 and 18).

(5) Supporting (schwannian) apparatus of a normal Wagner-Meissner corpuscle.

The production of palisades has been explained as a sort of accident (Francini). Instead of dividing transversely and aligning themselves behind one another along the length of the fiber, the nuclei are assumed to divide longitudinally and take their position in a plane perpendicular to the axis of the original cylinder. Thus, it is said, the nucleated palisade is constituted.

Fortuitous Palisades: In this conception there is both truth and error. There are palisades which are produced by this simple mechanism. I shall call them rudimentary or fortuitous palisades. In my opinion, the nuclei always divide longitudinally. If secondarily they move lengthwise along the cylinder, the cylinder elongates. If the dividing nuclei remain in the same transverse plane, the cylinder broadens without elongating. A simple palisade system is formed when two such nucleated planes arise near each other along the same cylinder. The cylinder does not elongate, but the longitudinal cleavage persisting in the middle of the internuclear cytoplasm and the subsequent appearance of the collagenous sheaths, completes a simple neurinomatous palisade.

In these rudimentary forms the nucleated and collagenous palisades have the general form of the cylinders. In fact, they are segments of cylinders comprising two nucleated palisaded discs separated by a disc consisting of their prolongations ensheathed in amorphous and fibrillar collagen. These fortuitous palisades usually remain small; the cylinder containing them is scarcely, or not at all broadened.

The palisades produced by this simple and fortuitous mechanism are to be found in almost all neurinomas.* I mention them especially in order to distinguish them clearly from the palisaded nodules which seem to me to be of much greater theoretical interest.

Palisaded Nodules: If all of the palisades in neurinomas were due to this simple and fortuitous mechanism, they too should have a cylindrical form. Whatever their dimensions, they should consist of alternate nucleated and collagenous discs, all the broader in proportion as their growth is prolonged. However, this discoid structure, real as it appears to be in compact and voluminous palisaded nodules, is an illusion soon dissipated by their examination in serial sections, especially when an edema occurs to dissociate the various

* I speak here solely of the compact bundles unmodified by degeneration of their sheaths (see Section III. Myxoid degeneration).

elements. The illusion is dissipated also by study of the histogenesis of the palisaded nodules.

On examining a palisaded nodule that has been dissociated by edema, it will be seen that each collagenous palisade does not really have the form of a disc included between two nucleated discs, but rather that of a long, sinuous cylinder, more or less flattened and branched, the branches anastomosing laterally with one another. Between these cylinders and applied to their surface there are branching cells, anastomosing, sheathed in blue, filling the interstices. The palisaded arrangement of the nuclei has disappeared.

The cylinders themselves are striated transversely by argyrophil fibers and by the ensheathed anastomotic prolongations of the cells which surround them. This cylinder and the cells which surround it form a structure exactly like the supporting apparatus of Wagner-Meissner tactile corpuscles, as their histogenesis shows.

Palisaded Meissnerian Nodules

In my edematous schwannoma of the palate, certain fortunate sections furnished images like those of Fig. 13. Locally a cylinder has elongated greatly and at the same time broadened. For simple mechanical reasons it has become curved. Its nuclei, instead of elongating lengthwise of the fiber, have elongated crosswise; they have aligned themselves along the sheath but their axes are perpendicular to it. The partitioning, at first cytoplasmic, secondarily collagenous, instead of forming longitudinally has formed crosswise, incomplete here as always, leaving the continuity of the syncytium intact.

The nuclei multiply, remaining marginal. The cylinder broadens and now the collagenous septa multiply also. They are no longer longitudinal, but transverse in relation to the cylinder. They divide the nucleated territories incompletely, ensheathing the prolongations which connect these nucleated territories from one side of the cylinder to the other. Here, as in the bundles, collagenization is more precocious around the cytoplasmic anastomoses than around the nuclei. Consequently at this stage the axis of the cylinder is surrounded by a series of marginal nuclei, but the axis itself is occupied by multiple anastomoses ensheathed in collagen uniting the nuclei transversely or, better, diametrically.

At this stage, when examined in a longitudinal and axial section,

the cylinder thus transformed constitutes a simple palisade system; but at the same time it has exactly the structure of an aneuritic Wagner-Meissner tactile corpuscle, such as I have described in pigmented moles, but a corpuscle that is prodigiously long and usually curved (Figs. 14, 15, 16).

There is one structural characteristic that distinguishes these aneuritic tactile corpuscles from normal ones. Having arisen from a member of a retiform system and being continuous with their fellows both longitudinally and crosswise, the corpuscles have preserved their initial anastomoses with neighboring cylinders, both at their ends and along their sides.* Like the tactile corpuscles of pigmented moles, they are situated in the course of the retiform cylinders, not at the end of simple nerve fibers like normal tactile corpuscles.

Figures 14, 15 and 16, taken from a neurinoma of the shoulder, which I owe to the kindness of Professor J. McFarland of Philadelphia, show how typical these Wagner-Meissner corpuscles may be. The tactile corpuscles rarely remain in this typical stage of their evolution. As a rule they increase in bulk and grow more complex. The marginal nuclei become superposed transversely (Fig. 17). Between them there appear new anastomotic prolongations ensheathed in collagen. In this way the complex palisaded nodule is constructed (Fig. 18 and Diagram 2, No. 4).

Discussion of Section II

From this point of view the palisaded nodules lose the accidental character conferred on them in the classic conceptions. They become organoid formations resulting from a special evolution of the fasciculated cylinders. It is well known that this evolution is not presented by all neurinomas. Elsewhere I shall revert to the frequency and the inconstancy of the differentiation of tactile corpuscles in tumors of the peripheral nerves, both encapsulated and diffuse. I have already called attention to the almost constant presence of these tactile corpuscles in pigmented moles and I have demonstrated thereby that these tumors spring from the tactile nerves of the derma. The tactile corpuscles of pigmented moles are derived from Schwann cells; they are seldom innervated.

* The anastomoses multiply by the customary process, longitudinal cleavage, at the same time that the palisaded nodule itself increases in bulk (Diagram 2).

What is logical for pigmented moles, is it not logical also for the encapsulated tumors of the nerves? May we not assume that those neurinomas in which the cylinders give rise to palisaded Meissnerian nodules have different organogenic properties from those neurinomas which do not produce palisades? In other words, is it not the tactile nerves that produce palisaded neurinomas? And are not non-palisaded neurinomas the product of non-tactile nerves, possibly motor nerves?

I know well that embryology, which has demonstrated the common origin of the entire schwannian system from the neural crest, does not yet authorize such an hypothesis; but the schwannomas in their two grand varieties confront us and demand an explanation. In default of two kinds of peripheral neuroglia, may we not suppose that the sensory and the motor neurites respectively, when they invade the initial cells of schwannomas before the beginning of their autonomous proliferation, in some way impregnate these cells, conferring on them and on their tumor-forming descendants specific organogenic properties? This is but another hypothesis, the experimental proof of which seems *a priori* unobtainable because laboratory animals, apart from the higher primates, possess no Wagner-Meissner corpuscles.

The Vessels

The vessels of neurinomas are capillaries. The vessel wall consists of endothelium resting on a thin collagenous sheath continuous with the collagen of the tumor. Often there are a few histiocytes in contact with this sheath. The intervals between the vessels are occupied by the compact tumor tissue already described in which the mesodermal (?) element is represented by the only cells of endoneurial type. I may remind the reader that these cells have not produced the collagen fibrils of the tumor; the collagen fibrils have been determined by the schwannian syncytium.

III. DEGENERATED FORMS

Sclerosis of Schwannomas

This much discussed sclerosis, which partisans of the schwannian hypothesis believe to represent connective tissue invasion of the schwannian tissue, has in reality quite other significance. It is the product of two successive and opposing processes, growth and decay.

(*a*) In growing, the bundles and the palisades become richer in collagen. Not only do the collagenous sheaths and fibrils multiply as new cylinders arise from the old ones, but also the cleavage which converts a cylinder into a bundle liberates a certain number of fibrils which were formerly included in the collagen sheath (homologue of the Plenk-Laidlaw sheath). These fibrils, having become interstitial, are the homologues of those which constitute the interstitial endoneurium of the bands of aneuritic regeneration. As described in Part I, this endoneurium is determined by the Schwann cells and not by the endoneurial cells which, when they exist, limit themselves to occupying the endoneurium secondarily.

(*b*) In areas where the tumor cylinders and the palisades cease to grow, some of the cells degenerate and disappear. The products of degeneration are often incorporated by macrophages which become filled with lipoid vacuoles like xanthoma cells and usually gather around the vessels. The origin of these macrophages is undetermined; they may be either endoneurial cells become phagocytic or histiocytes.

When the tumor cells disappear, the collagen fibrils which formerly surrounded them remain; they come closer together and slowly lose their argyrophilia as their colorability by picro-fuchsin and aniline blue increases. There seems to be no increase in their number but simply a change in their tinctorial affinities. That which proves their schwannian origin is the fact that for a long time the architecture of the bundles and of the palisades can be recognized when every cell has disappeared from their interstices (Figs. 19 and 20). The collagen fibrils come together, not because they have multiplied, but because the schwannian bands which formerly separated them no longer exist. In the interstices of this collagen framework, become more dense by the disappearance of the Schwann cells, there is often no cell whatever, endoneurial or any other kind.

Myxoid Metamorphosis

This state of degeneration is the one described by Antoni as Type B, the reticular type. It may be only partial, or it may affect the entire tumor. In extreme examples the neurinoma becomes cystic.

As for the genesis of Type B, I can only confirm Antoni's explanation, jellification and swelling of the collagenous fibrils and sheaths

of the cylinders and of the palisades. The sheaths disappear first, the fibrils next, commencing with the finest ones (Figs. 21, 24, 25); the collagenous palisades are affected last. The effect of this jellification is to separate the tumor cells without breaking their anastomoses; from this point of view it has the same effect as the 1 per cent solution of nitric acid used by Nageotte in the study of degenerated nerves. As in the acid, the jellification swells the endoneurial collagen and reveals the continuity of the schwannian syncytium in three dimensions. It has another and unexpected result. Deprived of their sheaths, which have become jellified, denuded and accompanied by a few collagen fibrils, the Schwann cells resemble and are mistaken for connective tissue cells, or for endoneurial cells. Nevertheless there can be no possible doubt of their origin: study of the bundles or of the palisades in process of jellification shows that it is really the cells of the cylinders and of the palisades that undergo this metamorphosis.

This myxoid transformation is always accompanied by profound changes in the blood vessels. The most constant lesion is hyalinization of the connective tissue coat proper of each capillary, a hyalinization which surrounds the endothelium with a sheath that may be very thick and may constrict or obliterate the lumen of the vessel (Fig. 25). To this hyalinization is often added local multiplication of the capillaries, forming here and there tiny glomeruli with hyaline walls very like those observed in many central gliomas.

It is probable that the myxoid transformation of neurinomas results from unfavorable circulatory conditions connected with this hyalinization of the vessels. It begins at a distance from the vessels, the tumor tissue in contact with the vessel still preserving its compact structure; but it ends by involving the tissue around the capillaries. It may be followed by atrophy and disappearance of the cells, in place of which there remains nothing but a fluid holding in suspension some fibrillar débris. The usual corollary to this cellular disappearance is the presence of lipoid macrophages around the vessels.

In certain instances this jellification of the sheaths is not accompanied by cellular atrophy; proliferation continues. It is obvious that it is not in tumors of this kind or in the areas presenting Antoni's Type B that one should seek to verify the description of the schwannian cylinders enclosed in their collagenous sheaths,

which I have given in the beginning of this paper. However, almost always the diagnosis of schwannoma may be made from the presence of typical cylinders which remain here and there, particularly around the vessels.

The Fibrils that Stain Blue in Phosphotungstic Acid Hematoxylin

In neurinomas, Mallory's phosphotungstic acid hematoxylin often stains some fibrils blue, usually very few. The American school offers this as an argument for the connective tissue origin of neurinoma. For them, these are fibroglia fibrils and as such they are assumed to be characteristic products of fibroblasts. However, it should not be forgotten that the very name given by Mallory to these fibrils, which are seen in connective tissue and especially in young connective tissue, is derived from their staining with this reagent exactly like the fibrils of central neuroglia. Nageotte has shown that the gigantic bands of experimental schwannomas contain fibrils colorable by Benda's method for neuroglia. For my part, in the same material I have seen fibrils, doubtless the same, stain blue with phosphotungstic acid hematoxylin. These fibrils belong to the Schwann cells and not to fibroblasts. At any rate, as far as this staining reaction goes, the fibrils found in neurinomas that stain blue with phosphotungstic acid hematoxylin might be neuroglia fibrils just as well as fibroglia. This reaction cannot serve as an argument either for or against the mesodermal or ectodermal origin of a tumor.

Summary and Conclusions

The aim of this paper is to demonstrate that the fundamental element of encapsulated neurinomas is structurally identical with the syncytium of Schwann when that syncytium is undergoing autonomous proliferation, a proliferation that has been released by the disappearance of the neurites which normally inhabit it.

The schwannian elements of a neurinoma proliferate within the endoneurium, bounded by the old perineurium, now become the capsule, and not in the extraneural connective tissue. This proliferation within the endoneurium explains why the bundles and their palisades are as free from individual lamellar sheaths (perineuria) as are the aneuritic bundles resulting from transformation of de-

generated fibers in the incised segment of a nerve (Experiment I) and in nerve grafts (Experiment II).

The palisaded nodules are no developmental accidents. They are organoid productions. Their histogenesis and structure are comparable to those of the schwannian supporting apparatus of the Wagner-Meissner tactile corpuscles.

Since the palisaded nodules are not found in all neurinomas, may we not ask if their presence or absence is not related to two different organogenic properties of the Schwann cells? Despite the single origin of the Schwann cells as they leave the neural crest, may there not evolve two peripheral neuroglias, a sensory and a motor neuroglia?

In the experimental schwannomas of the rabbit as well as in the spontaneous schwannomas of man, the collagenous framework of the schwannian bundles is determined by the schwannian syncytium and not by the endoneurial cells. The endoneurial cells occupy the framework secondarily.

In schwannomas the sole collagen of mesodermal origin is that of the vessel walls. All the rest of the collagen is determined by the neurectodermic syncytium.

The sclerosis of schwannomas does not result from their invasion by connective tissue but from condensation of the framework when deserted by the Schwann cells, and also at times by all cells.

For these many reasons, at the beginning of this paper I have insisted that neurinomas contain mesoderm only on the same terms as do central gliomas, no more and no less. I have no illusions of the fate in store for a doctrine so tainted with heresy. The universally held dogma that collagen is the direct and specific product of connective tissue cells, mesodermal by definition, will long confront me. Nevertheless this dogma is indefensible.

No cell, not even the fibroblast, produces collagen. As demonstrated by Nageotte, the fibroblast determines the coagulation of collagen in its vicinity but does not secrete it. Doubtless the cell operates by means of a ferment which coagulates an albuminoid of the interstitial substance to form collagen, just as a thrombocyte acts on the fibrinogen of the blood plasma by a ferment which coagulates it in the form of fibrin.

As far as it concerns the collagen of connective tissue, the exoplasm hypothesis maintained by Studnicka and by Laguesse is a

vitalistic sophism based on artifacts. However, if this hypothesis should ever have any basis in fact, it should be found in regenerating nerves and in schwannomas; for what is the membrane of Schwann, the delicate cuticle which borders the schwannian cytoplasm and which collagenizes secondarily, if not an exoplasm which has at least the merit of existing?

In reality, the collagenous framework of the bundles of regeneration and of schwannomas is not secreted, neither is it produced, either by mesodermal cells or by Schwann cells. It is determined by the Schwann cells just as basement membranes are determined by epithelium. In the light of these facts, it is probable that the classic conceptions of the mesodermal origin of the endoneurium should be revised.

I have once more to thank my friend, Dr. George F. Laidlaw, for the scrupulous accuracy of his translation and for his tireless industry in presenting my ideas to the English-reading medical public.

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DESCRIPTION OF PLATES

PLATE 67

FIGS. 1 and 2. Schwannoma of the palate. Edematous region. Trichrome stain.

Isolated bundle of schwannian cylinders, most of them cut across. All of them are enclosed in a continuous collagen sheath (blue) intimately adherent to their cytoplasm. Their caliber varies greatly. The broadest cylinders present either one nucleus (*a*) or several nuclei in an isogenic group (*b*). Almost all of the cylinders present collagenous septa, either rudimentary in the form of spurs projecting inward from the sheath or in the form of lines in the middle of the cylinder. This partitioning is finished early around the cellular prolongations (*c*); it proceeds more slowly around the isogenic nuclear groups (*b*). Partitioning is followed by cleavage of the collagenous septa (*e*). The cleavage converts the primitive cylinder into a bundle (*d*). (*f*) Endoneurial cells. (*g*) Simple cylinders.

FIG. 3. Schwannoma of the palate. Non-edematous region. Silver impregnation of the reticulin (Laidlaw) followed by staining with the ponceau-acid fuchsin mixture, phosphomolybdic acid and acetic light green.

In this very thin section (2 microns) the cytoplasms seem to be vacuolated. In reality they are almost colorless. The red lines cutting the cylinders are the cytoplasmic septa which little by little turn into collagen; in this way the solid cylinder is cut up into a bundle as in Figs. 1 and 2. The sheaths and the collagenous septa instead of being blue seem to be formed of two substances, the one amorphous, colored green, the other fibrillar and argyrophil. The argyrophil fibrils seem to be embedded in the green substance.

The letters (*a*), (*b*), (*c*), (*d*) and (*e*) have the same significance as in Figs. 1 and 2. At (*g*) note two giant bundles with groups of isogenic nuclei. The bundles are in process of partitioning but not yet split apart. The

green and black collagen appears in the heart of the schwannian syncytium. At no point in the preparation or in serial sections of the same bundle is there a single endoneurial cell to be found. All of this collagen therefore is determined by the syncytium of Schwann alone.

On the right and below are three small schwannian cylinders of the same preparation highly magnified (× 1800). Partitioning is more advanced in the non-nucleated region. On the right there is substitution of collagen (green) for the red cytoplasmic septa. The argyrophil fibrils are embedded in the green collagen sheath.

FIG. 4. Schwannoma of the palate. Edematous region. Trichrome stain.

Schwannian cylinders growing longitudinally (*cf.* Experimental Schwannomas, Part I, Fig. 5). Retiform arrangement. The cylinders show distinct striation, especially between the nucleated regions, all the more pronounced since each red striation (protoplasmic prolongation) is ensheathed in blue (*a*) (rudiments of palisades). The nuclei are dividing by amitosis into isogenic groups (*b*), which break up rapidly as the nuclei range themselves in rows along the fiber. Around the cylinders in the edematous tissue there are several inflammatory cells.

FIG. 5. Schwannoma of the palate. Edematous region. Trichrome stain.

Palisade system. The nuclei are arranged in three planes, (pl 1), (pl 2), and (pl 3), (nucleated palisades). The cytoplasmic bodies of each plane are connected with those of neighboring planes by slender anastomotic prolongations ensheathed in collagen. They are retiform, all elongated in the same direction and grouped in small bundles. The ensemble of these collagenous sheaths (see their real structure in Fig. 6) constitutes the classic fibrillar and collagenous palisades which separate the nucleated palisades.

(*a*) Mononuclear cytoplasmic body.

(*b*) Amitotic division of a nucleus and formation of an isogenic group.

(*b'*) Isogenic group; the uppermost cell begins to separate from the others.

(*c*) Ensheathed anastomotic prolongations.

(*c'*) Cross-section of bundles of cytoplasmic prolongations uniting two isogenic groups belonging to plane 1 (pl 1) but situated below and above the section. These groups of nuclei, now separated, had a common origin in the same primitive isogenic group.

(*b''*) A cell of group (*b'*) shifts longitudinally and parts from its fellows in order to occupy another plane, where it may become the point of departure of another nucleated palisade situated between (pl 1) and (pl 2).

FIG. 6. Schwannoma of the palate. Non-edematous region. Trichrome stain.

Palisaded nodule growing both longitudinally and transversely. On both sides of the center of the figure, palisaded systems superposed and cut in various planes; (*l*) longitudinal; (*t*) transverse; (*o*) oblique. In each nucleated palisade the nuclei are ranged not only crosswise (staves of a barrel) but also lengthwise; this indicates lengthening of the cell which contains them. The lengthening of the cell makes preparation for the appearance of new collagenous palisades in the present nucleated palisades.

fig. 1

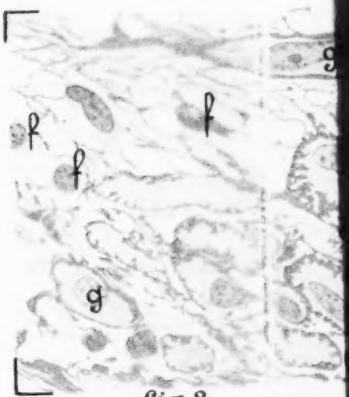


fig. 2

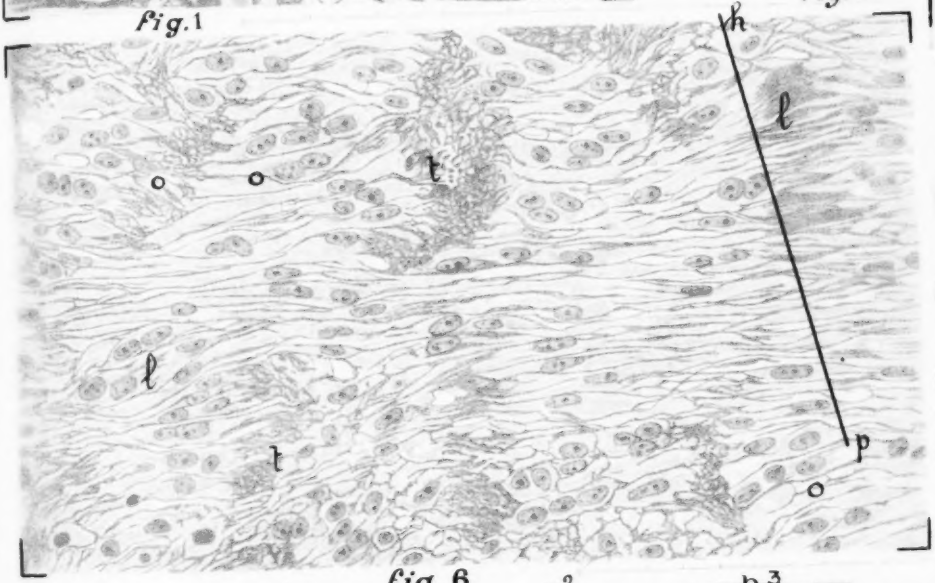
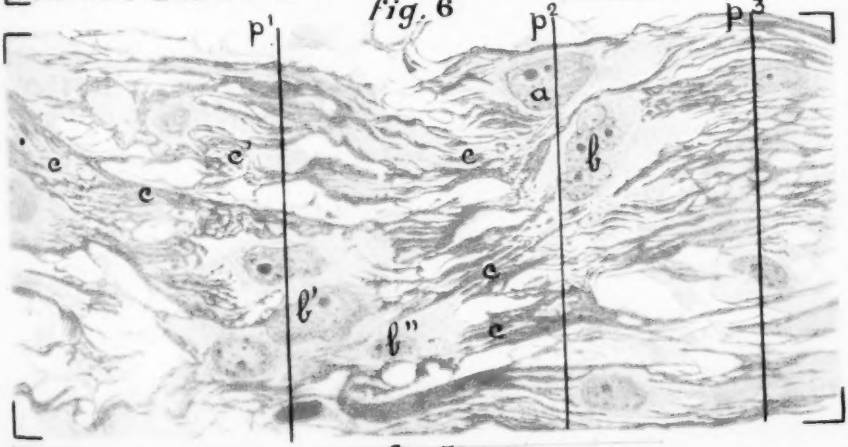


fig. 6



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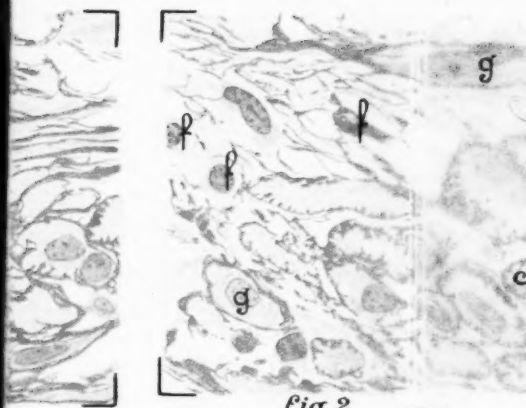

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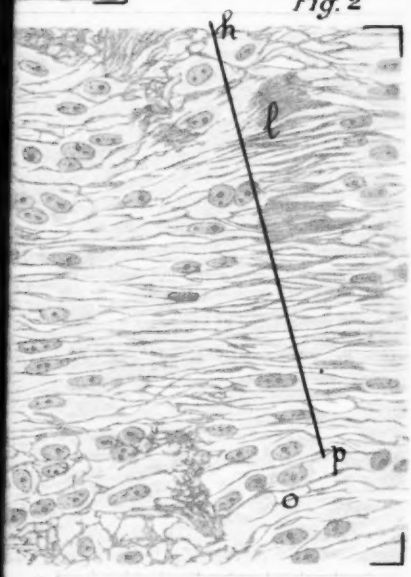


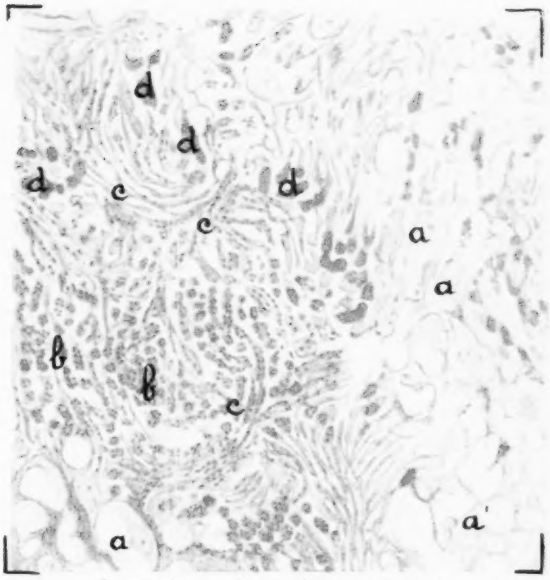


fig 7

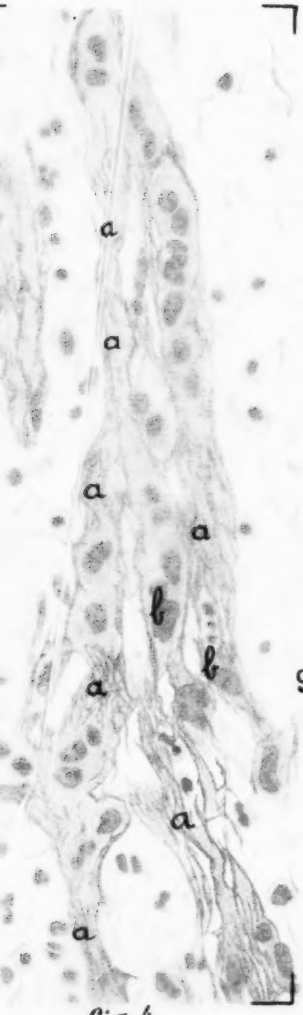
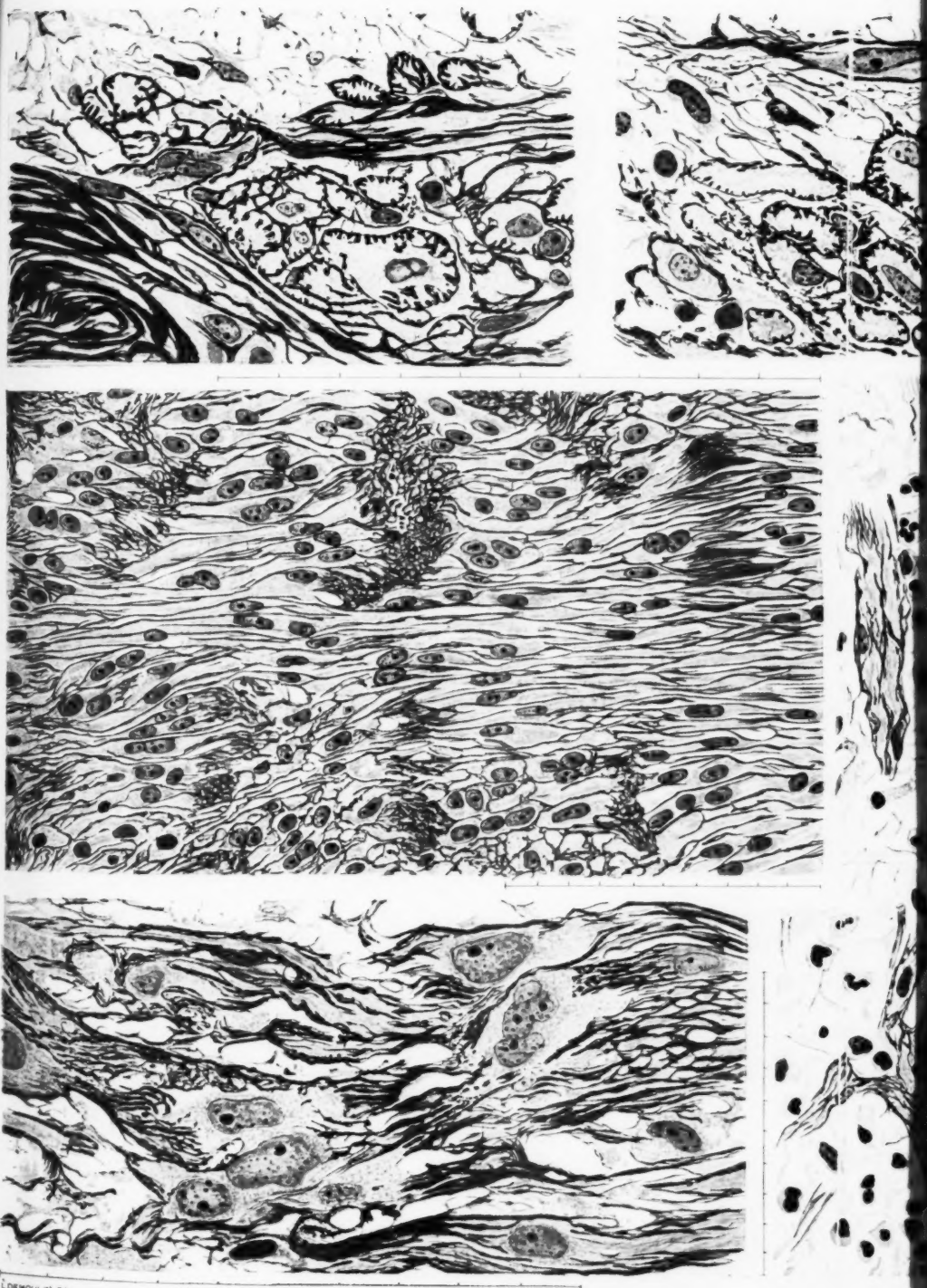


fig. 4

fig. 3

C. CONSTANTIN



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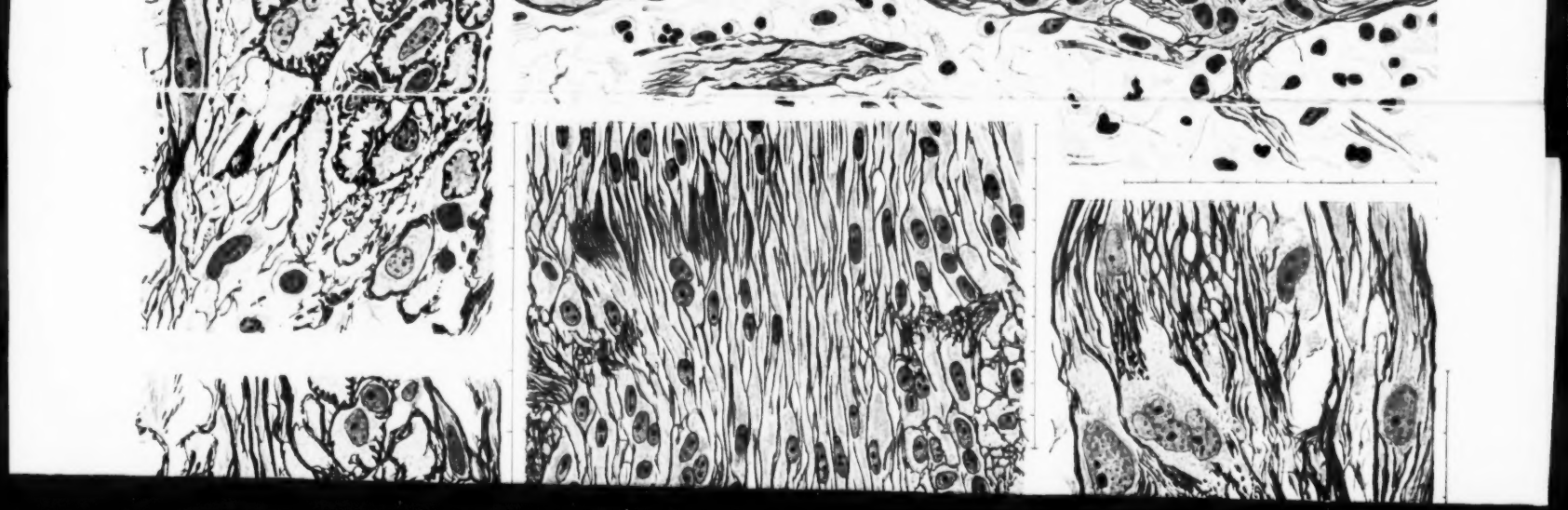

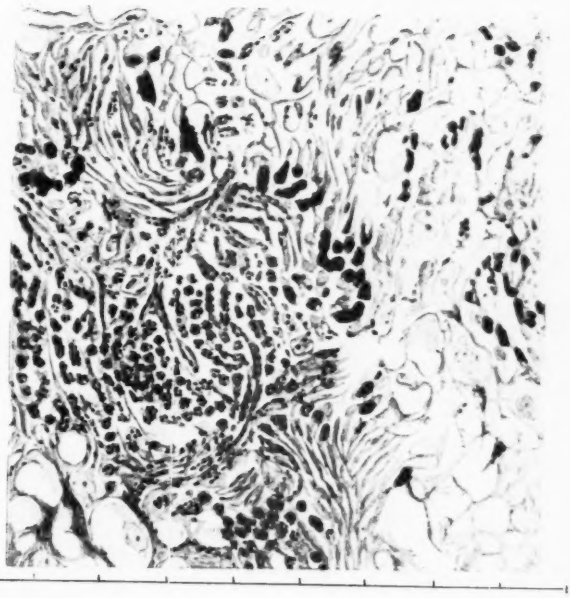

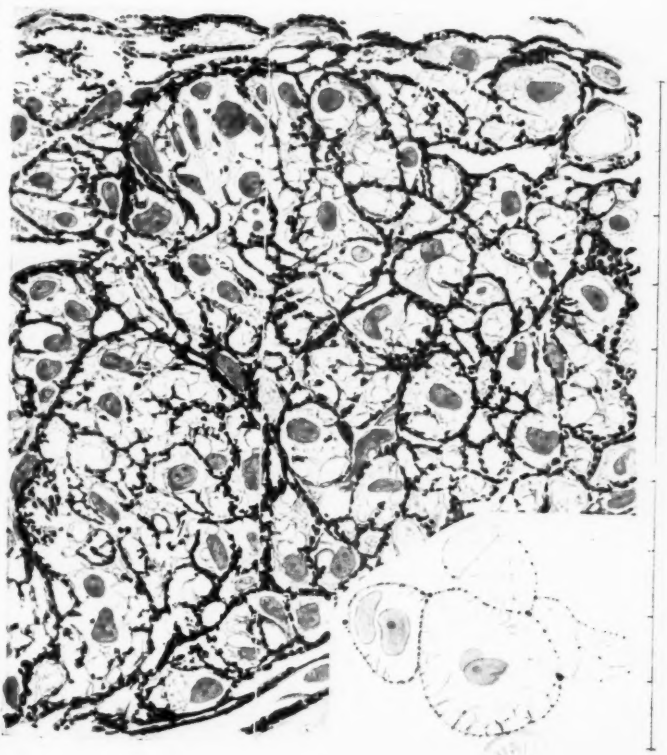

C. CONSTANTIN

Experimental and Spontaneous Schwannomas. II

In the center of the figure the elongation exists almost alone and constitutes a typical straight bundle in the heart of the palisaded nodule. Just as the palisades take their origin from the bundles, so the bundles may spring from the palisades.

FIG. 7. Schwannoma of the cervical region. Beginning of atrophy. Laidlaw silver-ponceau-acid fuchsin-light green.

Palisade of irregular type, lozenge-shaped, cut perpendicularly to the general direction of the plane of the palisades. The line of section is that of line h–p on the tracing of Fig. 6.

(*a*) Palisaded nuclei embedded in cytoplasm. The cytoplasmic territories are separated by incomplete collagenous septa which respect the transverse anastomoses. A certain number of cells have disappeared, leaving their collagenous niches vacant (*a'*).

(*b*) "Collagen fibers" directly connecting two nucleated palisades situated above and below the section. These fibers have been cut across. Each fiber is complex and contains an axial red dot, the cross-section of a minute protoplasmic cylinder, ensheathed in green. In the green sheath are seen black dots which correspond to cross-sections of reticulin fibrils. These so-called "collagen fibers" then are really minute prolongations of the cells belonging to and connecting the two superposed nucleated palisades, each prolongation being sheathed both with amorphous collagen and with reticulin.

(*c*) Other oblique and branching prolongations establish lateral anastomoses between nucleated palisades and between their prolongations.

(*d*) These black spots correspond to bundles of collagen fibers; their brush-like ramifications furnish the argyrophil fibrils visible at (*a*) (see Fig. 19).

Plate 68

Fig. 8. Schwannoma of the palate; very edematous region. Trichrome stain.

On the left a cross-section of a group of bundles. The nucleated territories are separated incompletely by collagenous septa. The partitioning is more complete in the bundles that are cut across between the groups of nuclei (rudiments of palisades). On the right a group of bundles cut a little obliquely. In the center of the group, young cylinders are completely split and separated from one another. Below bundles in process of elongation cut lengthwise. In the interstitial edema are several isolated cells without sheaths; these are endoneurial cells.

Fig. 9. Schwannoma of the palate; slightly edematous region. Trichrome stain.

Slightly oblique section of a complex palisaded group in lozenge form. Above, the section passes through the nuclei, which are incompletely separated by collagenous partitions. Upper center, the border of a collagenous palisade similar to the one in the center.

In the center is a "collagenous" palisade constituted in reality by collagenous tubes containing cellular prolongations. In the center of the figure the tubes are cut across; they connect two nuclear planes, one above and the other below the level of the section. In the lower part they are oblique, connecting nucleated planes above and below the level of the section.

Fig. 10. Schwannoma of the palate; very edematous region. Trichrome stain. × 1500.

Cross-section of a sclerosed palisade. The cellular prolongations ensheathed in collagen are recognized as tiny black circles. Some of them are free; most of them are united in small bundles. The collagen fibrils appear as lines or dots. On the left these fibrils seem to be embedded in the tubular sheaths of the cellular prolongations.

Fig. 11. Schwannoma of the palate; non-edematous region. Laidlaw silver-ponceau-light green.

Longitudinal section of a bundle. The cylinder in the center presents a slight shrinkage on each side of which the nuclei are spaced lengthwise. At the point of shrinkage the collagenous sheath is visible in front view. Note the web of criss-cross argyrophil fibrils which constitutes it. In the meshes a gray tint (green in the section) represents the pellicular collagenous membrane in which the fibrillar net is embedded.

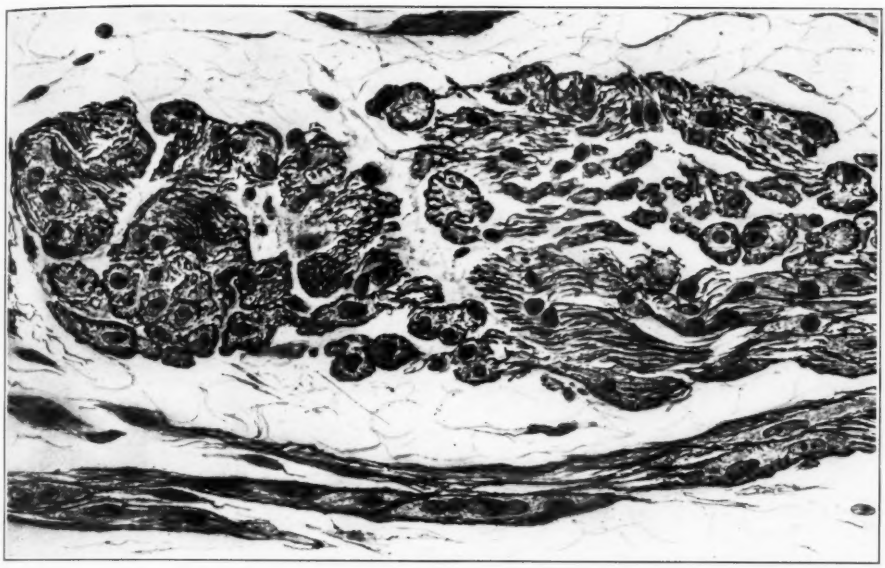

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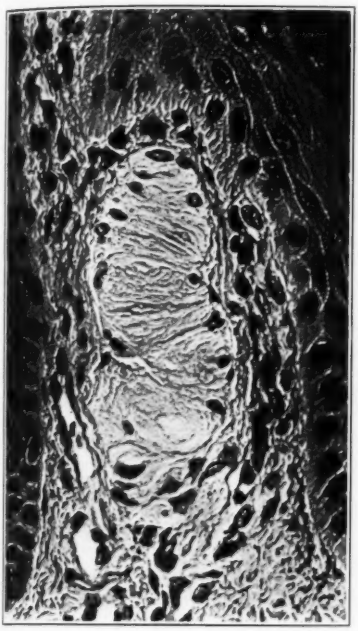
PLATE 69

FIG. 12. Pulp of index finger. Normal Wagner-Meissner corpuscle.

FIG. 13. Schwannoma of the palate. Beginning of the evolution of palisades. Long, curved and broadened cylinder. The nuclei are marginal and oriented perpendicularly to the sheath. Between them appear collagenous septa, no longer longitudinal but transverse.

FIGS. 14 and 15. Typical meissnerian evolution.



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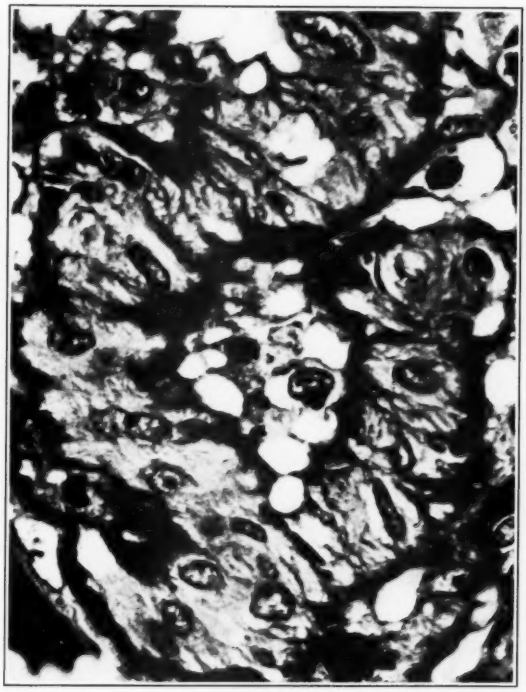

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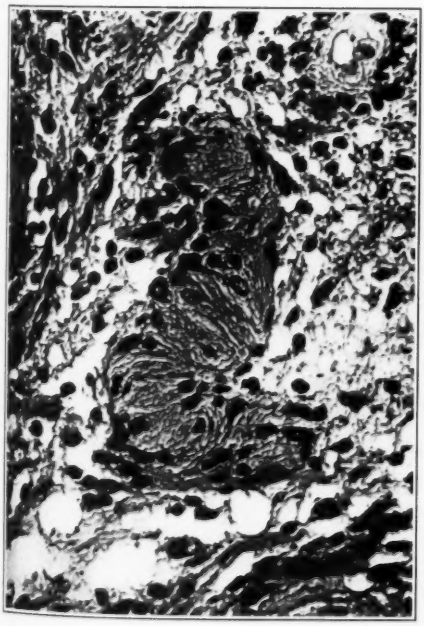

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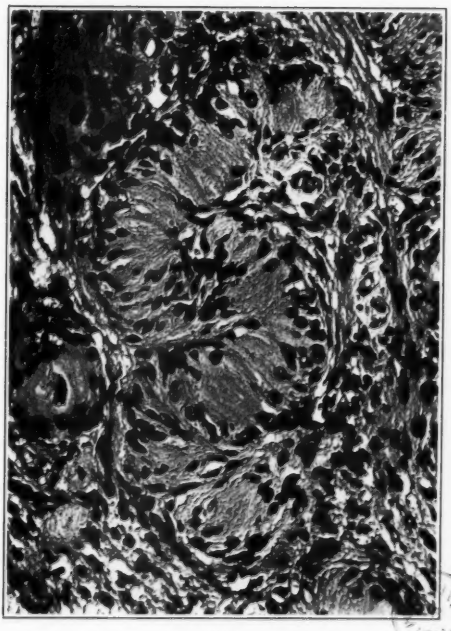

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Masson

Experimental and Spontaneous Schwannomas. II

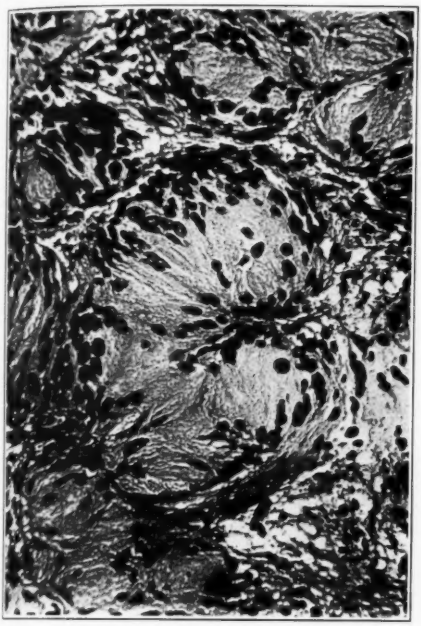
PLATE 70

FIG. 16. Broadened meissnerian corpuscle. The collagenous palisading becomes more pronounced.

FIG. 17. Intermediate form between a meissnerian corpuscle and a typical palisaded nodule. Beginning of the formation of a secondary palisade.

(FIGS. 14, 15 and 17 were taken from the same preparation of a neurinoma of the shoulder which I owe to the kindness of Professor McFarland, of Philadelphia.)

FIG. 18. Schwannoma of the palate. Complex palisaded nodule.



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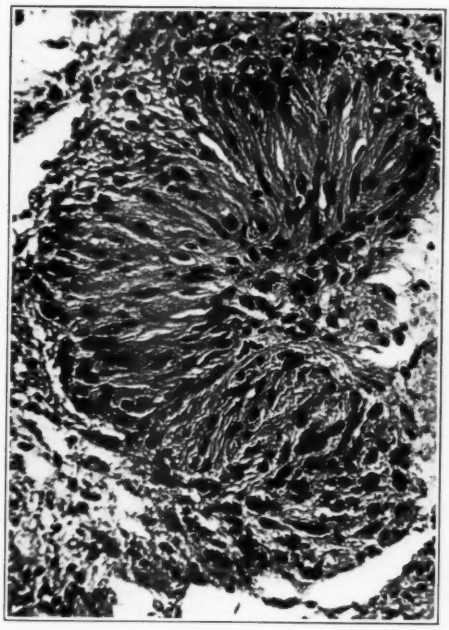

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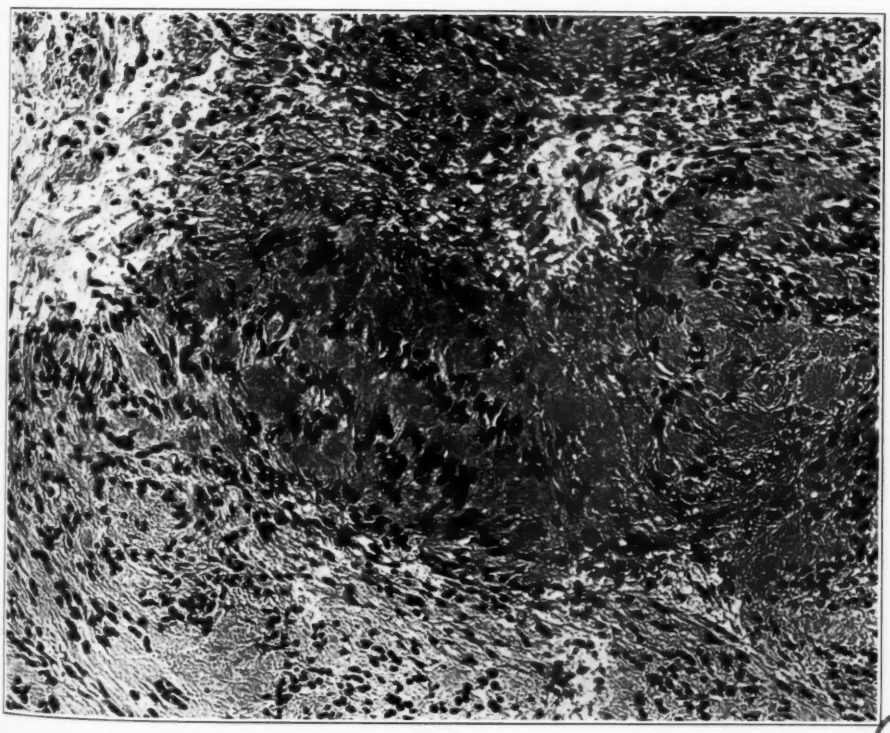

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PLATE 71

FIG. 19. Schwannoma of the palate. Laidlaw silver-ponceau-acid fuchsin-light green.

Sclerosis of a palisade. Rarefaction of the tumor cells. Persistence of the collagen. The gray tint corresponds to collagen sheaths almost entirely deserted. The figure shows particularly clearly the arrangement of the argyrophil collagen in the palisaded systems.

FIG. 20. Schwannoma of the cervical region. Trichrome stain.

Total sclerosis; slightly edematous region. There are no more cells but only the collagenous framework of the neurinoma. Here all argyrophilia has disappeared. Nevertheless in the upper part of the figure we recognize the characteristic arrangement of the palisaded systems and below the arrangement of the bundles.

FIG. 21. Schwannoma of the forearm. Trichrome stain.

Beginning jellification of the collagen in a bundle. Beginning of Antoni's Type B. The sheaths and the interstitial fibers have become indistinct. The cylinders are separated by an amorphous substance stained feebly by the aniline blue.

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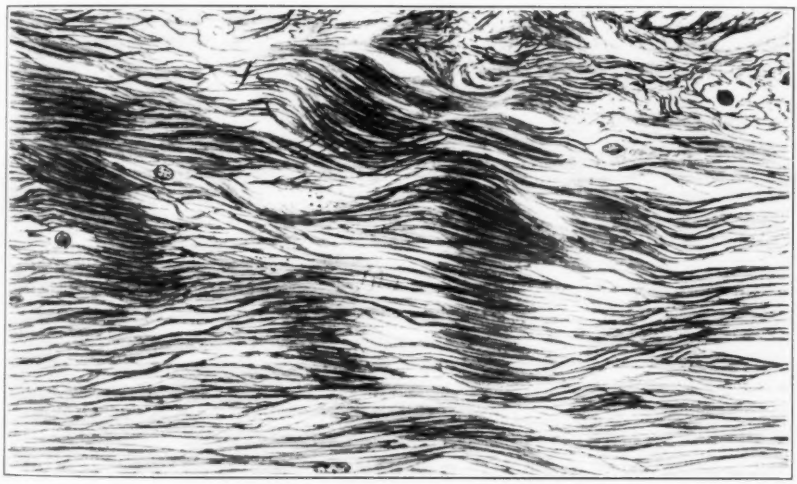

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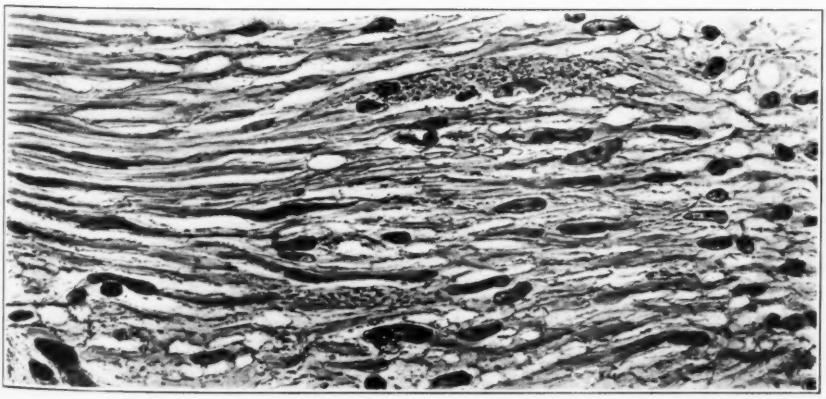

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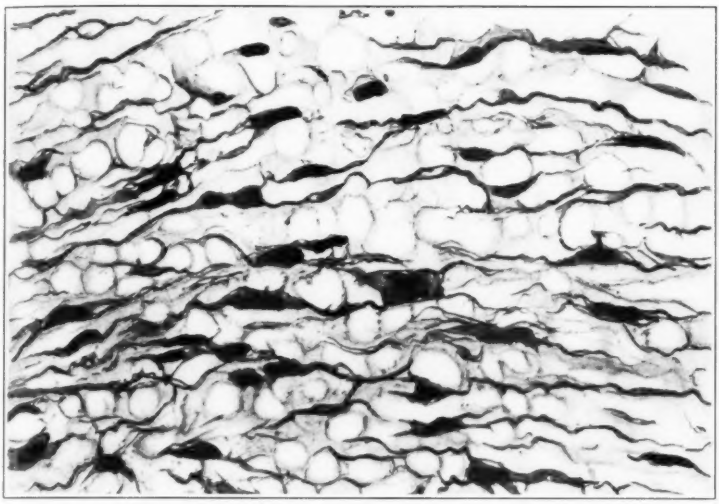
PLATE 72

FIG. 22. Schwannoma of the forearm. Trichrome stain.

The same bundle. The region represented lies to the right of that seen in Fig. 21. The cells, while remaining anastomosed and fasciculated, are separated by the amorphous bluish substance. They no longer have a sheath. A few bluish, swollen fibrils are recognizable with difficulty. This is a perfect example of Antoni's Type B.

FIG. 23. The same tumor. Trichrome stain.

Cross-section of a jellified bundle. The figure shows the anastomoses which connect the prolongations of the same cell with one another and also the anastomoses of the cell with its neighbors. At this stage the Schwann cells are distinguished with difficulty from endoneurial cells. The three-dimensional retiform structure of the schwannian syncytium is particularly clear. The silhouettes of the cells represented in these two figures recall strangely those of oligodendroglia.



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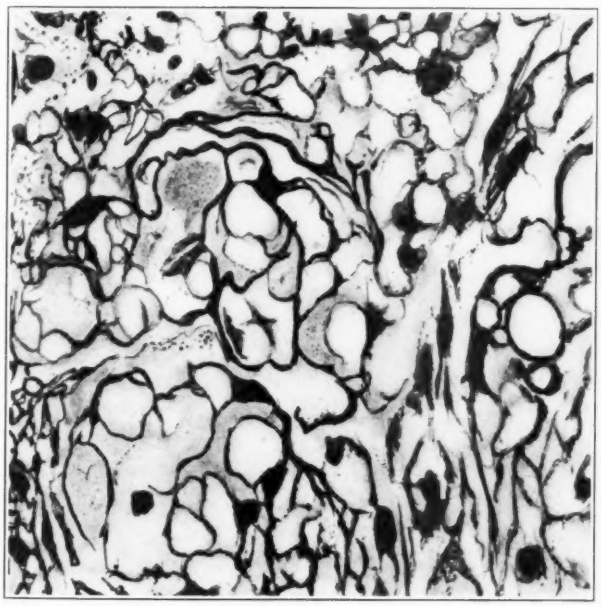

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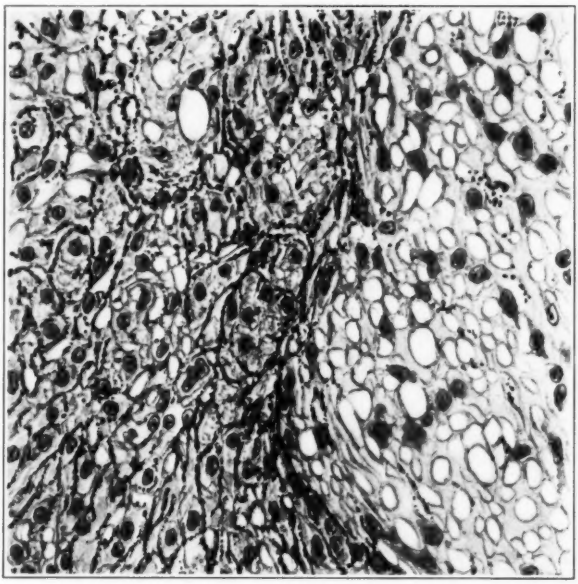
PLATE 73

FIG. 24. Schwannoma of the forearm. Laidlaw silver-ponceau-acid fuchsin-light green.

On the left a cross-section of a compact bundle. The sheaths are a little thickened. Cross-sections of argyrophil fibrils are seen clearly as dots. On the right a jellified bundle. The cylinders no longer have sheaths. The argyrophil fibrils have become scanty. Cavities mark the places of the autolyzed cells.

FIG. 25. Schwannoma of the forearm.

Antoni's Type B. Hyalinized vessel forming glomerular groups. In the cartouche, one of these groups more highly magnified. The lumen of a knotted capillary has been cut across at four different points. This vascular arrangement is very frequent in certain central gliomas.



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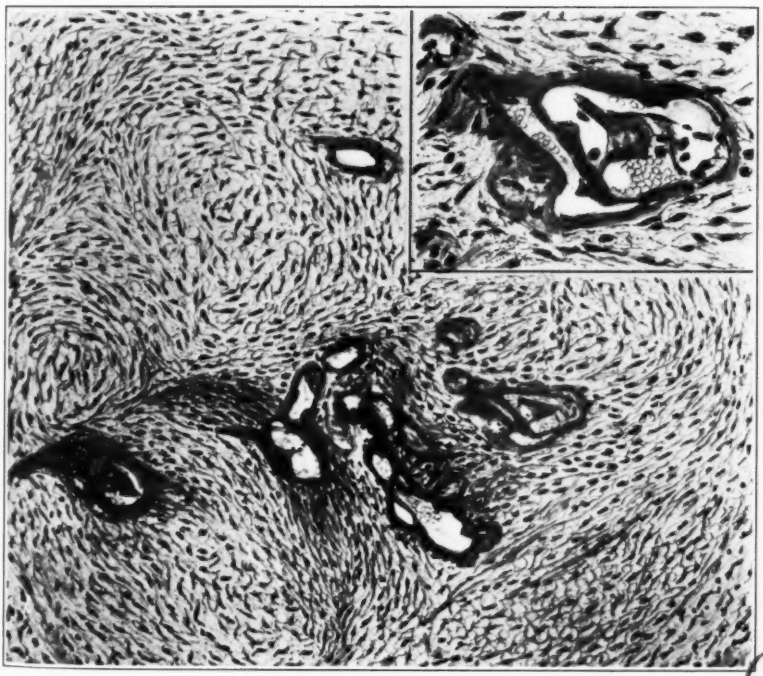

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Masson Experimental and Spontaneous Schwannomas. II

THE ORIGIN OF EPITHELIUM-LINED BLOOD CYSTS (CHOCOLATE CYSTS) OF THE OVARY FROM THE GRAAFIAN FOLLICLE AND ITS DERIVATIVES*

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The epithelium-lined blood cysts of the ovary have been discussed extensively during the last three decades under various terms, of which the most important are adenoma endometrioides ovarii,[1] perforating chocolate cysts,[2] ectopic Müllerianoma,[3] adenomyoma of the ovary,[4] endometriosis,[5] endometrioma and endometriomyoma.[6] The majority of these terms tacitly assume that the material comprising the cysts is aberrant endometrium. Pick's term "endometrioides" emphasises the similarity of the tissue to the endometrium of the uterus. "Adenomyoma" is a noncommittal term and the suggestion of the "perforating chocolate cysts" is unsatisfactory in view of the ambiguity (from the pathological point of view) surrounding the term "perforating." I would submit, for reasons to be given, that the term "multiple chocolate (or tarry) cysts" is sufficiently descriptive and does not wed us to any hypothesis, which in the light of new observations may have to be abandoned.

A number of hypotheses have arisen to explain these cysts, of which the most important are those of Iwanof and Sampson. The former postulated a metaplasia and downgrowth of the surface epithelium of the ovary, and in other regions, of the peritoneum. Sampson suggested an actual transplantation of endometrium from the uterus to the ovary and other organs.

In 1929 the writer [7] brought forward evidence showing that many of these cysts arose from the bodies normally occurring in the ovary — namely, the graafian follicles and their derivatives. At first, proof of this hypothesis could not be obtained in all cases, and in 1930 the similarity of tarry cysts to examples of endometriosis (the nature of which could not be demonstrated) was discussed.[8] Later, further evidence was obtained in the case of the previously unproved examples. In another paper [9] the subject was considered

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in further detail, giving some of the evidence for the view stated, and the disabilities of the implantation were discussed.

In the present contribution it is proposed to elaborate the thesis by consideration of the mechanism of the transformation of several forms of follicles into epithelium-lined blood cysts.

The primitive form of the graafian follicle — the primordial follicle — consists of the ovum with one layer of cells of the stratum granulosum. As the follicle becomes mature, these cells proliferate until they are several layers thick. Later a cavity (the antrum folliculi) appears and the ovum, surrounded by cells of the stratum granulosum, projects into this (Fig. 1). At this stage the cells of the stroma immediately surrounding the follicle swell and become spheroidal, constituting a theca interna, and around this the stroma cells arrange themselves in a layer which is described as the theca externa.

The changes that occur normally and which may result in the formation of the cysts to be considered are those of proliferation and evolution on the one hand, or retrogression on the other. The former process gives rise to the corpus luteum and can only take place in a completely mature follicle which has ruptured, with projection of the ovum into the peritoneal cavity. The retrogressive changes which result in the formation of the atretic follicle in its various forms occur in the great majority of follicles.

A reference to many current books and papers indicates that the significance of these bodies is not generally appreciated. Atretic follicles are confused with graafian follicles, the hyaline and fibrous bodies arising from them — the corpus candicans, corpus fibrosum, and so on — are intermixed with the corpus albicans, and the occasional bodies in which the cells come to resemble luteal cells are most often confounded with the corpus luteum. It will be apparent that, in the absence of a knowledge of these structures, the accurate interpretation of pathological conditions occurring in the ovary is impossible.

In my experience, the multiple blood cysts may show morphological characteristics which correspond to any of the bodies occurring normally in the ovary. Also, although relatively few main paths are followed in the development of the blood cysts, at the same time very many by-ways may be taken in the production of what are finally similar results. The life history of the maturing graafian follicle may

be divided into two stages: (1) before an antrum folliculi is formed, and (2) after the formation of the follicular cavity. These will be considered separately.

The Primitive Graafian Follicle

The examination of the retrogressive changes in the primitive follicles of the human ovary is difficult, but in the case of ovaries of animals in which the ova are large (fish, reptiles, birds and, of the mammals, the Monotremata) the changes may be followed with ease. Subsequent examination of higher mammalian and particularly human follicles is thereby facilitated.

The ovum disintegrates and this appears to be the primary morphological change. The cytoplasm stains more deeply, becomes vacuolated and the nucleus becomes first pyknotic and then disintegrates. The cells of the stratum granulosum invade the ovular material, remove it by phagocytosis and finally the cells hyalinise, giving rise to a small hyaline body known as the corpus restiforme.

The pathological variant of this process is the formation of a small cyst, owing probably to some modification in the mechanism of absorption of the ovular material. Usually the cyst remains of a comparatively small size.

If the stratum granulosum has become three or four layers thick, some of these cells disintegrate and disappear so that a single layer is to be found. In many cases there is little evidence, except for the nature of the surrounding structures, for the determination of the origin of the small cyst, but in other cases there are remnants of a theca interna which make its nature certain. Though they are usually spherical, partial collapse of these cysts gives rise to various appearances in sections. When these structures occur in the ovaries containing "endometrial" cysts, they contain blood and are lined by a single layer of cuboidal, and rarely columnar, cells which often possess cilia. It is of interest that some of the earlier accounts of "graafian follicles" contain a reference to ciliated cells lining the cavity.

The Maturing Follicle

The vast majority of the graafian follicles present in the ovary do not become mature, but undergo atresia. Just before the time of ovulation a number of follicles are approaching maturity. The rup-

ture of one of these is accompanied by the retrogression of the others. This has been shown experimentally, in birds by Pearl and Surface [10] and in rodents by Herrmann and Stein,[11] to be due to the presence of a hormone produced by the developing corpus luteum. Since the number of times that ovulation in any ovary occurs is limited (300 to 500) and there are many thousand ova in the organ, the reason for the tremendous excess of bodies derived from atretic follicles over those arising from true corpora lutea is apparent. These bodies are, therefore, much more important — at least numerically — than the corpora lutea.

Various forms of retrogression are encountered:

1. Absorption.
2. Atresia with cystic development.
3. Atresia with proliferation of the stratum granulosum and cyst formation.
4. Atresia with proliferation of the stratum granulosum without cyst formation.*

1. Absorption: The commonest mode of retrogression of the graafian follicle takes place *in situ* with the least amount of disturbance of the surrounding tissues. The ovum dies, the stratum granulosum proliferates and, in lower animals, forms projecting masses beneath the zona pellucida. The granulosa cells invade the zona pellucida and the ovum. The membrana limitans becomes thicker and the cells of the theca interna proliferate. These gradually hyalinise, giving rise to a fibrous body possessing a hyaline capsule. This is termed the corpus atreticum. Characteristically it is composed of a central zone of material resembling connective tissue and a peripheral zone of hyaline tissue. The collapse of this body, which usually occurs, results in the corpus candicans. Occasionally some disturbance of the normal mechanism results in the production of a morphological variant — all or most of the tissue being fibrous with little or no hyaline material. Such a body is designated a corpus fibrosum.

Sometimes small spaces arise in one or another part of these structures. These may occur in either fibrous or hyaline bodies. It has

* One form of atresia observed in lower animals, described as rupture atresia, [13] in my experience does not appear to have a constant correlative in the human ovary. The rupture of many of the atretic follicles containing blood, which is so characteristic of the multiple tarry cysts, is a possible counterpart.

been suggested that the cells which line such a space are endothelial in origin. Occasionally, however, a number of the cells of the stratum granulosum remain and the lining cells may be seen to be continuous with these.

Well marked, epithelium-lined glands may be found in such relationship to masses of hyaline and fibrous material as to suggest that they arose from the spaces referred to, and indicate that they arose from the follicle which gave rise to the hyaline or fibrous material. The significance of such masses in juxtaposition to glands described as "endometrial" has apparently been overlooked or regarded as incidental by observers.

2. *Atresia with Cystic Development:* The formation of follicular cysts, varying from the size of a pin-head to one-half inch or more in diameter, is an everyday observation to investigators of ovarian histology and pathology. The frequence of their occurrence causes us to regard them as being a normal method of retrogression of the graafian follicle.

The changes which take place imitate those occurring without cyst formation. The ovum disintegrates and the cells of the stratum granulosum begin to disappear also. The cumulus disappears at an early stage, and thus is formed a cyst lined uniformly by a layer of granulosa cells three to five layers thick (Fig. 2). At the same time the theca interna proliferates and forms a well defined layer outside the stratum granulosum. With further retrogression the stratum granulosum becomes still more reduced until only one layer is to be observed. The theca interna remains in its well developed state. Hyaline change usually occurs in the theca interna and the membrana limitans may be very well developed. It is important to appreciate that both hyaline and fibrous changes, which were described in regard to the absorption of the follicle *in situ*, may occur here. Usually some of the theca interna remains as a recognisable structure, but when it is replaced completely by hyaline and fibrous tissue the recognition of the nature of the cyst may be difficult. A knowledge of these transformations and the discovery of all gradations between the follicle commencing to undergo atresia and the cyst with only hyaline material in the wall, render the identification of structures of doubtful origin practicable.

While these changes are progressing, alteration in the shape of the cyst takes place. Apparently absorption of the cyst contents occurs

and collapse of the cyst results in a crenation of the wall. A characteristic appearance is obtained on section.

Atresia is frequently associated with haemorrhage, particularly in the region of the theca interna (Fig. 5), but in some cases, especially in the ovaries which are the site of the epithelium-lined blood cysts, bleeding occurs into the cavity of the cyst (Fig. 4). It is stated in the literature that blood does not find its way into the cavity of the atretic follicle, but an examination of the typical atretic follicles in the ovaries mentioned above will reveal some which show this peculiarity.

When blood finds its way into the cavity of these cysts, an epithelial * lining develops. Apparently the presence of blood is necessary for the development of this lining. This epithelium appears to arise from the few remaining cells of the disintegrating stratum granulosum. The reasons for this conclusion are: (*a*) the epithelium occurs in the cysts at the same site as the stratum granulosum, *i. e.* just internal to the theca interna; (*b*) rarely both may be found in the same cyst; and (*c*) the cells are epithelial in nature, *e. g.* they possess cilia.

Examination of the walls of a series of cysts thus shows all gradations between atretic follicles with a well developed stratum granulosum and theca interna without blood, and those which contain blood and show some degenerative changes in the wall on the one hand, and the hyaline and fibrous cysts either with or without an epithelial lining on the other. At first the stratum granulosum is about five layers thick and the theca interna is composed of well formed spheroidal cells. Then the stratum diminishes in size though the theca remains markedly in evidence. Finally the stratum becomes one layer thick, though still recognisable as such. At some stage blood appears in the cavity. Epithelial cells now appear at the site of the stratum granulosum and seem to arise from it. They may be syncytial at first, but for a time, even after cell boundaries are obvious, the cells are very irregular in form (Fig. 6). Later the cells become definitely cuboidal or columnar. The origin and nature of such a cyst is beyond doubt because the theca interna is still well marked (Figs. 3 and 4). Lastly there are those cysts in which the

* It is to be appreciated that the term "epithelium" is used only in the most general sense. The ovarian structures are derived from the coelom and are thus mesothelial in origin. The argument that epithelium does not give rise to phagocytic cells (with which incidentally I disagree, but do not propose to discuss here) does not apply.

epithelium is indistinguishable from that of the "endometrial" cysts and there is an underlying fibrous cellular stroma. Often the general conformation of the cyst suggests a relationship with the atretic follicle even in absence of other evidence (compare Fig. 5 with Figs. 12 and 13).

The distinguishing feature of the first two methods of atresia is a relatively large development of the theca interna. In the next two groups the atretic processes are characterised by a disproportionate overgrowth of the stratum granulosum, so that the resulting structure may bear some relationship to a corpus luteum.

3. *Atresia with Proliferation of the Stratum Granulosum and Cyst Formation:* The most characteristic form in which overgrowth of the stratum granulosum takes place is in the multiple luteal cysts associated with hydatidiform mole. Atresia of a large number of follicles occurs and results in bodies, of greater or less size, sometimes solid but more frequently cystic which resemble, both in their general structure and in the nature of their cells, corpora lutea; hence the term — multiple "luteal" cysts. When it was appreciated that the process was one of atresia, the principal group of cells was thought to arise from the theca interna as in the other forms of atresia mentioned. The work of several investigators, however, showed that these cells arose by proliferation of the stratum granulosum. These "luteal" bodies undergo retrogressive changes similar to those seen in the atretic follicles of the normal ovary, and fibrous and hyaline bodies result.

Haemorrhage occurs into some of the cysts, the number of which varies in different specimens. As in the case of other blood cysts of the ovary, physicochemical changes gradually occur in these blood cysts, resulting in a change of the blood to a tarry or chocolate consistence.

The walls of these cysts are frequently lined by a definite epithelium (Fig. 8). In these structures particularly can the continuity of this epithelium with the luteal cells (*i. e.* the modified stratum granulosum) be demonstrated.

In addition to these multiple cysts, similar cysts may occur in some ovaries singly in a sporadic fashion. They may contain blood which gradually becomes tarry. Retrogressive changes take place in the wall, the "luteal" cells become fewer in number and atypical in appearance, and the tissue adopts a fibrous or hyaline character.

These cysts have been described by a number of writers. An excellent account is given by Shaw.[12] He points out that the cells which, though atypical, resemble true luteal cells, may arise from both the stratum granulosum and the theca interna. The cysts containing derivatives of both layers he refers to as "tarry granulosa luteal cysts," and those in which all remnants of the stratum granulosum have disappeared as "tarry theca luteal cysts."

Typical examples of each of these varieties are easily diagnosed, but many intermediate cases occur. Probably some of the tarry theca luteal cysts arise directly by luteinisation of the cystic atretic follicles described in the preceding section, but others arise by complete disintegration of the granulosa representative of the tarry granulosa luteal cyst. Brakeman and Shaw have described the occurrence of a heterotopic epithelial lining in such cysts. They have referred, however, mainly to the large single and double cysts which are generally recognised as being luteal. I would emphasise here that similar, though smaller, cysts occur amongst the multiple, epithelium-lined blood cysts described as "endometriomatous."

The sporadic cystic corpora lutea atretica occur in two principal forms: (1) the cysts in which the tissue closely resembles luteal tissue; and (2) the cysts in which the cells are very atypical even at an early stage.

(1). In the first group the cysts are easily recognisable since the cells resemble typical luteal cells, but the marked festooning of the cyst wall, characteristic of the derivatives of the true corpus luteum, is absent. Degeneration of the cells and their replacement by fibrous and hyaline material results in atypical appearances, but all gradations are to be found and experience enables one to interpret even the most atypical forms. Haemorrhage may occur into these cysts at any stage and a heterotopic epithelial lining frequently develops. It is of importance that both the retrogressive changes and the development of the epithelium are relatively late results in the life history of the cyst, and thus the epithelium is to be found in most imposing form in those cysts in which there is least evidence of the nature of the cyst. This is in all probability the reason for the opinion that the multiple, epithelium-lined blood cysts are not of local ovarian origin.

The retrogressive changes occurring in the walls of these cysts do not occur uniformly and in some cases it is possible to find luteal

tissue in one part of the wall, hyaline tissue obviously of luteal origin in another, and material indeterminate in character in another. This circumstance and the discovery of gradations between the typical "luteal" cyst and the epithelium-lined blood cysts determines the follicular origin of the "endometrial" cysts beyond doubt. Hyaline tissue is frequently described in the walls of blood cysts by the protagonists of the implantation hypothesis.

(2). The atypical forms comprise a group in which the walls are lined by large cells with small nuclei and voluminous vacuolated protoplasm. The cysts undoubtedly arise from luteal bodies of the atretic series. The problem is the nature of the cells.

These cells are undoubtedly phagocytic in character. They arise in greatest numbers in those cysts in which haemorrhage has apparently occurred at an early stage. The question is whether they are histiocytes or derived from the luteal cells.

There is not sufficient evidence at present to enable one to dogmatise upon this point, but I am of the opinion that the cells are derived from the luteal cells (usually the derivatives of the stratum granulosum) for the following reasons:

(*a*) The phagocytic activity of the cells of the stratum granulosum in some forms of atresia, in lower animals, is undoubted.[13]

(*b*) The morphology of such cells is that of typical phagocytes (of histiocyte type). This is a morphological change dependent on a change of function.

(*c*) Evidence of remnants of both layers — stratum granulosum and theca interna — is to be found and the cells of both layers are atypical and resemble phagocytes.

(*d*) Where luteal cells and phagocytic cells are found together intermediate forms may be seen.

(*e*) Gradations from typical follicles showing similar cells which are obviously of granulosa origin to the atypical varieties described here are found.

These cysts develop a heterotopic epithelial lining. This lining may be present only in one part of the cyst, it may completely cover the wall or it may be patchy in distribution. The epithelium * in some cases is continuous with the phagocytic cells (Fig. 10).

* See footnote on page 422.

4. Atresia with Proliferation of the Stratum Granulosum without Cyst Formation: This results in the production of small bodies consisting for the most part of cells indistinguishable from the phagocytic cells described above. Degenerated cells, débris arising from the breakdown of these and blood cells, and at times considerable amounts of well formed red corpuscles occupy the centre of these structures. They seem to arise in non-cystic atretic bodies into which small haemorrhages occur at an early stage.

This form of atresia is described here as a separate variety and well formed bodies are characteristic, but all gradations are found between these and the cystic forms referred to above.

Small spaces arise in some of these bodies. The débris found in the centre of the structure contains cholesterol and related substances, and the phagocytic cells unite to form syncytial masses around the material. Distension of the space occurs until the peripheral cell mass is but one layer thick. On the wall of some of the larger spaces an epithelium definite and columnar is found (Fig. 9).

The Corpus Luteum

After rupture of the mature graafian follicle, the stratum granulosum commences to proliferate to an astounding degree, giving rise to the large mass of cells comprising the convoluted walls of the luteal body. The cells also enlarge until they become the characteristic luteal cells. The theca interna also proliferates and gives rise to an irregularly placed layer of "paraluteal" cells. The central cavity may contain a considerable amount of connective tissue, but a space containing fluid, even though small, is almost invariable. The spot at which the graafian follicle ruptured on the surface heals, but it can usually be recognised as a depression of the exterior of the organ and by the projection of the corpus luteum towards this site.

Four stages of development may be recognised.

1. Stage of Proliferation or Hyperaemia: The granulosa cells begin to luteinise, but at this stage the theca interna cells look much more like the adult luteal cells. The corpus luteum is, at this stage, an inconspicuous vesicle of greyish colour — usually flattened.

2. Stage of Vascularisation: The luteal layer becomes invaded by newly formed capillaries pushing in from the theca interna. Whether haemorrhage does or does not occur at this stage is a much debated

question. It probably does take place in some cases, though most authorities deny its occurrence until the next stage.

3. *Stage of Maturity:* The zenith of this stage is reached just before menstruation commences. It is now the characteristic yellow body of text-book description. The well formed luteal cells are separated from the lumen by a more or less well marked layer of connective tissue. The theca interna is represented by the collections of cells described by Pinto as "paraluteal." Haemorrhage occurs into the cavity of the body.

4. *Stage of Regression Marking the Onset of Menstruation:* There is a shrinkage of the luteal layer and fatty degeneration of the cells occurs. It is the presence of the fat in the cells which is responsible for the yellow colour of the "typical" corpus luteum. The cells now atrophy — pyknosis and ultimately disintegration of the nuclei occur. Connective tissue cells advance from the theca zone into the luteal layer and gradually replace the cells. Hyaline tissue appears, but whether this occurs in the connective tissue or in the luteal cells is as yet undecided. (I would subscribe to the second view.)

In the final stage the replacement of the luteal tissue by hyaline material is complete. The body produced is known as the corpus albicans. This is characteristic, but the corpus candicans arising from the atretic follicle is frequently mistaken for it. The corpus albicans, however, is usually larger, is composed of larger convolutions of hyaline tissue and possesses evidence of a central cavity.

Cysts of the Corpus Luteum

Cysts of the corpus luteum, at an early stage, show typical luteal tissue in the wall. As the cyst becomes older this tissue becomes replaced by hyaline material and, as happens in the case of the atretic follicles, sometimes by fibrous tissue. These changes are to be found in the older cysts and the fibrous tissue is best developed in the cysts which have become distended.

Should the luteal tissue become uniformly and completely replaced by hyaline tissue a corpus albicans cyst is formed. Many variations depending on the type and extent of the change taking place in the luteal tissue may arise.

Any of these cysts may contain blood and, as the cysts age, changes occur in the blood resulting in the formation of chocolate or tarry material. Haemorrhage takes place into the cysts from time to

time so that tarry material and fresh blood may be seen occasionally in the same cyst.

Corpus luteum cysts may be lined by the luteal cells, by a connective tissue layer internal to the luteal cells, or by a heterotopic epithelium lying internal to the connective tissue — as pointed out by Fraenkel.[14]

Since relatively so few graafian follicles mature and rupture on to the surface, only a few corpora lutea are formed, and therefore cysts arising from this structure are found much less commonly than those derived from the atretic follicle. Furthermore, the characteristic feature of ovaries, which are the site of "endometrial" glands and cysts, is the observation that all the bodies found in the organ are undergoing retrogression [9] — immature and mature follicles of various forms are affected. It would appear that no follicles are allowed to come to maturity during the active stage of the disease; some factor, possibly excess anterior pituitary hormone or related substance, is causing atresia and haemorrhage in all the follicles.

However, in the ovaries which contain multiple blood cysts, an occasional cyst of definite corpus luteum origin is to be found. Such cysts are always ancient.

Cysts of the corpus luteum are usually large, but quite minute though perfectly formed derivatives are to be found in the ovaries mentioned. The relationship of such structures to a healed stigma reveals their nature even when other criteria of differentiation are absent.

Résumé

A great many structures occur in the ovary derived from the graafian follicle, most of them by the process of atresia, some by way of evolution and the corpus luteum. It is not practicable at present to give a complete account of all possible forms, but it is intended to draw attention to some of them. So many changes are still without adequate explanation, and the amazing number of appearances are so intricate and difficult of elucidation that a finished statement is not attainable.

The principal feature is that cysts of very many varieties may possess an epithelial lining and some of them, without thorough study of the ovary, will not be referred to their correct relationship with the follicles.

This brings us to the question of terminology. Since they arise from the numerous bodies of the ovary a general term is desirable. The term luteal cyst is applied to several forms of the larger cysts. Follicular blood cyst is applied to a different condition and does not include the derivatives of the corpus luteum. The most characteristic macroscopic features are their multiplicity and their blood content. Therefore, until their origin and nature are fully understood and recognised, the term "multiple chocolate (or tarry) cysts" seems adequate.

The Epithelium

The epithelium lining these cysts may be flattened, cuboidal or columnar. Each type of epithelium may be found lining a cyst completely, or all varieties with gradations between them may be found in the same cyst. In early examples the epithelium is nearly always flattened, but in older cysts (the age being shown by the presence of hyaline material) the epithelium becomes columnar. The characteristics of the columnar epithelium, which suggest that it plays a part in an absorptive mechanism, will be dealt with in another paper.

The origin of the epithelium lining tarry luteal cysts has been a source of speculation for a considerable time. Three possible origins have been suggested, namely: (1) from the surface epithelium of the ovary growing in at the stigma of the ruptured graafian follicle; (2) from endothelium by metaplasia; and (3) from luteal cells or their precursors the cells of the stratum granulosum.

The first can apply only to corpus luteum cysts and seems undoubtedly to be the explanation in some cases, since it is possible to trace the epithelium of the cavity in continuity with the surface epithelium. The endothelial origin does not seem to be adequate when some of the characteristics of the epithelium — the tall columnar form and the presence of cilia — are considered. The characteristics suggest an origin from epithelial cells and the writer is satisfied that the evidence definitely establishes the luteal (or granulosa) origin of the heterotopic epithelium for the majority. Even in the cases in which the epithelium develops from the surface epithelium, the cells are probably comparable with those lining luteal bodies arising from atretic follicles, since the stratum granulosum and the luteal cells are genetically related to the surface epithelium.

The epithelium may be found in three circumstances: (1) where the epithelium completely lines the interior of the cyst; (2) where only a portion of the cyst is so lined; and (3) where the epithelium lines part of the cyst and is in direct continuity with granulosa or luteal cells which are lining the wall elsewhere.

Subepithelial Stroma

Beneath the epithelium there develops a loose tissue containing small round cells, spindle cells, obvious phagocytic cells and some pigment. The comparison of this tissue with similar material lining non-epithelialised blood cysts and in which absorption of the cyst contents is occurring, suggests that this tissue is taking part in the absorption of the blood. Its degree of development is closely associated with the development of the columnar character of the epithelium.

This stroma is frequently likened to the stroma of the uterine mucosa. Actually this is more a gross than an intimate histological resemblance.

The first stage in its formation appears to be a swelling of the subepithelial tissue, extreme vascularity and accumulation of fluid — "oedema." Some observations suggest that this may be dependent on some alteration of cyst tension (Fig. 12), though this idea is difficult of application in many cases. That alterations of tension are present is shown by the collapse of the cysts. The areas described frequently occur on the portion of the wall which projects into the cavity.

Later and sometimes without the intervention of the preceding stage, a number of small round cells accumulate and some of the connective tissue cells swell. Phagocytic cells containing a large amount of protoplasm with varying amount of blood pigment and possessing small nuclei appear.

Gland Formation

"Gland" formation may occur in two principal ways: (1) from small atretic follicles — each follicle becoming a gland space; and (2) as subsidiary formations from larger cysts.

Of the second variety, the simpler form is that due to distortion of cysts which have collapsed. The distortion of the wall results in the formation of crypts. These crypts, if cut obliquely in section,

give an appearance of glands. These are to be found particularly towards the end of longitudinally collapsed cysts. Another method of formation is a definite outgrowth of the epithelium into the surrounding tissue. That this is an active process seems certain from the observation that often the glands extend beyond the confines of the cyst wall, *i. e.* beyond the boundaries of the hyaline tissue. They may be traced for considerable distances and at times a gland space near the surface of the ovary may be shown, by serial section, to be actually continuous with a comparatively deep cyst.

Complications Due to Proximity to the Surface: It has been tacitly assumed by Sampson and other protagonists of the implantation hypothesis that the presence of glands near the surface of the ovary indicates an implantation of material on the surface of the organ. Actually the observations are to be explained as a rupture of primary ovarian cysts. The occurrence of glands derived from the immature follicle near the surface of the organ has been mentioned. In a similar manner glands arising from atretic follicles of greater development, in which epithelial activity is marked, occur near the surface and alterations of intracystic tension, such as rupture, affect the development of the lining (Figs. 12 and 13). Such rupture may be followed by a projection outwards of part of the inner wall (Fig. 14), and this gives a clue to the origin of the gland and stroma débris found on the surface of the organ. Portions of the original cyst wall can frequently be seen (Fig. 16). These features may be absent from one section, but serial sections should be made in such cases before conclusions are drawn.

Comment

These observations are only a few of those to be encountered in the examination of ovaries containing blood cysts. No doubt the extraordinary variations found in the structure of the walls of the cysts has been responsible for the opinion that the epithelium, which is such a constant feature, is the most important. That extreme variation of structure of the bodies of the ovary derived from the graafian follicle occurs normally may be determined by a study of a number of organs. These bodies have been insufficiently examined and their relationship to the blood cysts has not been appraised, and thus the significance of the epithelium has not been appreciated.

In the majority of current descriptions emphasis is laid on the

epithelium without due regard to the other parts of the cysts. It has been assumed that because some of the cysts do not possess epithelium they have previously possessed such a lining, and by some process (*e. g.* pressure atrophy) have lost it. The opposite view, that these cysts are an earlier stage in which the epithelium has not yet formed, should be seriously considered.

The labour expended by many investigators on the multiple blood cysts has established them as a clinical entity and has attracted attention to their special features. The conception of aberrant endometrium, however, of whatever origin, helps us but little in understanding the condition from the pathological point of view.

The transplantation of apparently normal tissue with its growth in the new situation requires some further explanation of its occurrence. Because the endometrium has special physiological reactions it has been argued that its pathology will be peculiar to itself. The corollary of this view is that pathological principles will be legion — there will be special processes for every organ in the body. This leads us into an untenable position.

On the other hand, in the hypothesis submitted in this paper, we are dealing with known, and for the most part, definite physiological phenomena and with fundamental and well known pathological principles.

The changes in the graafian follicle are well recognised, though some of the more abstruse manifestations still require elucidation. The process of atresia has been shown to be due to hormone activity, in some cases arising from a corpus luteum, but also in others from other parts of the body — particularly the anterior pituitary gland. It has also been shown by several experimental physiologists that the haemorrhage which occurs into the body of the ovary is the result of several factors, one of which is a hormone of the anterior pituitary gland.

The particular factors which are active in the human being are still undetermined, but, in the lower animals, I have ascertained experimentally that the anterior pituitary hormone may produce atresia and haemorrhage in the follicles and that, in many cases, the presence of the blood is associated with the development of an epithelial lining. This is to be discussed in another paper.

From this it would appear that the development of the epithelium is the result rather than the cause of the bleeding into the cysts.

In a case recently observed (to be described elsewhere) typical cyclical menstrual bleeding occurred in ovarian cysts of proved ovarian origin. From this point of view it might be noted that the haemorrhage, often cyclical, which occurs in the non-epithelialised follicles and luteal bodies of the ovary has been disregarded by the authorities who uphold the "endometrial" hypothesis of the nature of the epithelium-lined blood cysts.

Conclusions

1. In the course of its development, the graafian follicle gives rise to a very varied series of structures, the advanced stages of which bear little or no morphological resemblance to the parent structure. A study of the intermediate stages is necessary for the demonstration of the relationship of the atypical forms to the original follicle.

2. Haemorrhage occurs so frequently into these structures as to be almost a normal phenomenon.

3. A heterotopic epithelial lining develops in the older cysts which contain blood. Since these older cysts, as stated, bear but little resemblance to the original follicles, the relationship has been overlooked.

4. These cysts are identical with those which, on account of the nature of the epithelium, have been described as "endometrial."

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DESCRIPTION OF PLATES

PLATE 74

FIG. 1. A typical graafian follicle showing an antrum folliculi, a cumulus containing the ovum and a well developed theca interna. The theca externa is comprised by those stroma cells which are arranged concentrically around the theca interna. S. = stratum granulosum. T. I. = theca interna. E. = theca externa. × 40.

FIG. 2. A retrogressing follicle showing a well preserved theca interna (T. I.). The stratum granulosum (S.) is only one cell thick. × 35.

FIG. 3. A small cystic atretic follicle which contained blood. The stratum granulosum (S.) is commencing to adopt an "epithelial" character. The follicular nature of the cyst is shown by the presence of the theca interna (T. I.). × 45.

FIG. 4. A higher power view of a small atretic follicle containing blood. The stratum granulosum is represented by a single layer of flattened and cuboidal cells. The theca interna (T. I.) can still be recognised. × 65.

FIG. 5. A collapsed atretic follicle showing a retrogressing stratum granulosum (S.) and a well marked theca interna (T. I.). There is a large extrafollicular haemorrhage (H.) in the left lower quadrant. Compare with Fig. 12. × 40.

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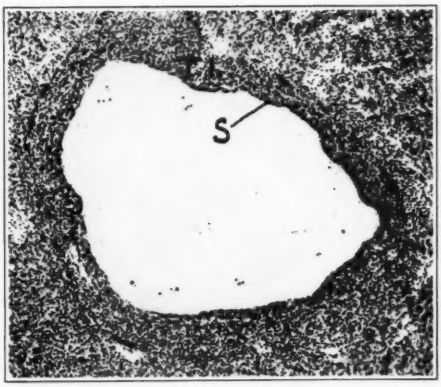

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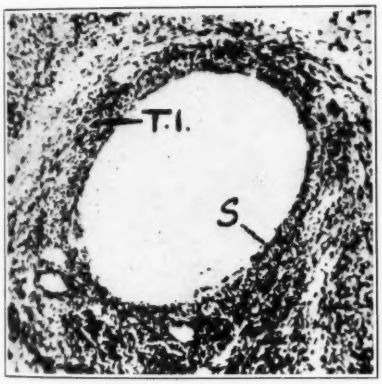

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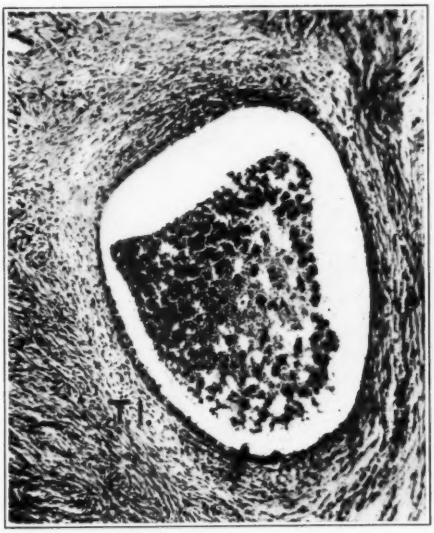

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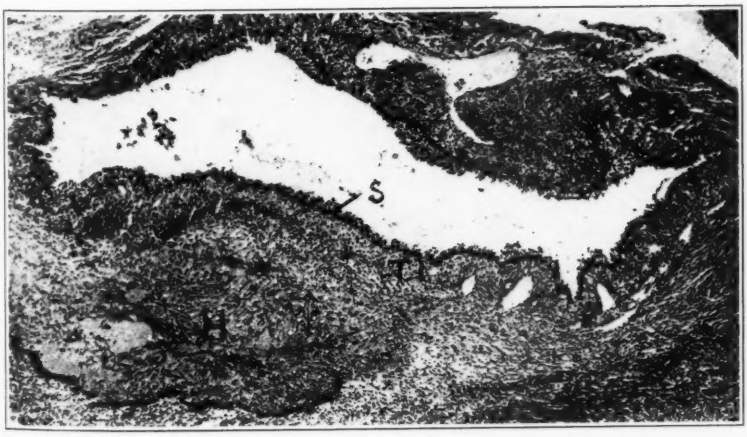

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Plate 75

Fig. 6. Portion of the wall of a follicle containing blood. The remnant of the stratum granulosum is adopting an epithelial character. × 200.

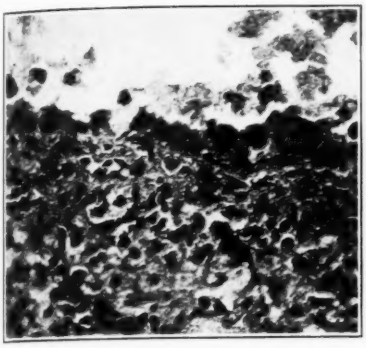
Fig. 7. Portion of the wall of a cyst of follicular origin showing the development of "glands" which were shown, by serial section, to be continuous with the cyst. × 50.

Fig. 8. Portion of the wall of a luteal cyst occurring, amongst many others, in association with hydatidiform mole. The epithelial lining is composed of cuboidal cells. × 90.

Fig. 9. A well developed epithelium-lined cavity which has arisen in an atypical atretic body, the greater part of which is composed of phagocytic cells (P.). × 25.

Fig. 10. Portion of the wall of a cyst of luteal origin. There are numerous phagocytic cells which are in close association with the epithelium. × 100.

Fig. 11. Portion of the wall of a cyst of luteal origin showing the development of glands by crypt formation. × 50.



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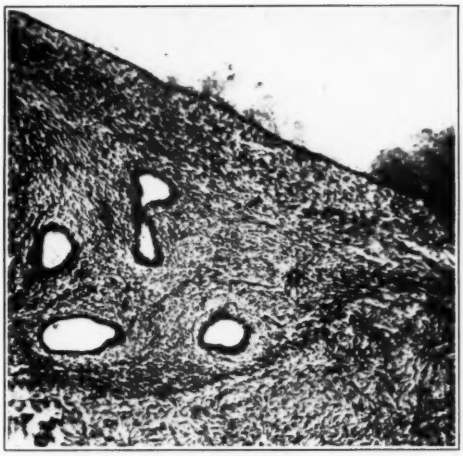

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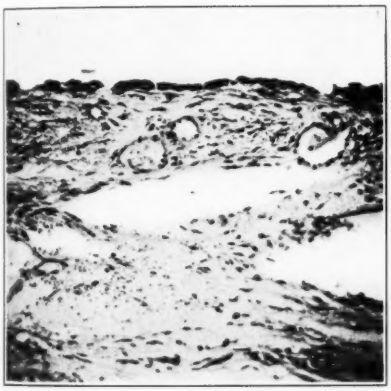

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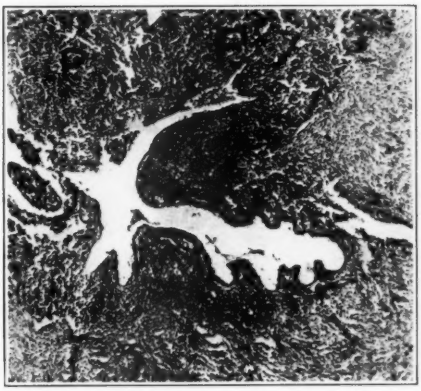

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11

King

Origin of Epithelium-Lined Blood Cysts

Plate 76

Fig. 12. A cyst of follicular origin which has just ruptured onto the surface of the ovary. Note the projection of the epithelium on the deeper side of the wall and the swelling and haemorrhage into the subepithelial tissue. × 25.

Fig. 13. A small cyst near the surface of the ovary, of follicular origin (serial sections showed that other portions of the wall possessed characteristic stratum granulosum and theca interna). Haemorrhage has occurred into the subepithelial tissues. Compare with Fig. 5. × 40.

Fig. 14. A ruptured cyst in which the epithelium and subepithelial tissue of the deeper wall have formed a marked projection outwards. The glands present are due to an exaggeration of the process observed commencing in Fig. 13. × 15.

Fig. 15. An appearance regarded as being evidence for the implantation hypothesis. This tissue arises by disintegration of the projection shown in Fig. 14. In this case portion of the original cyst wall is to be seen at the left-hand edge (W.). × 12.

12

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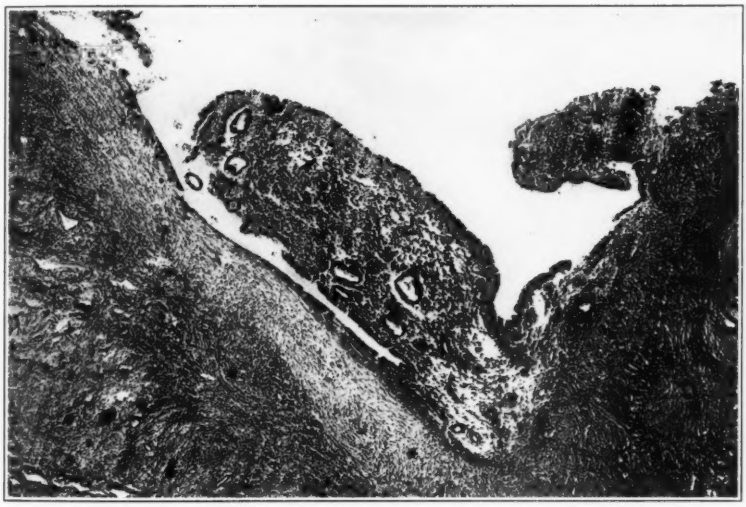

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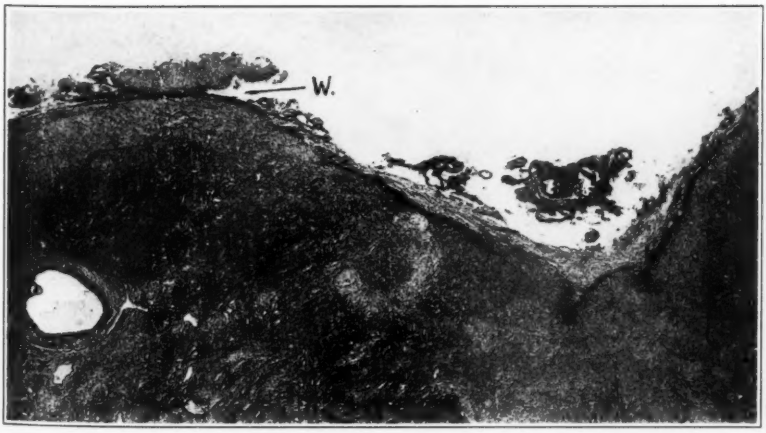

15

MELITENSIS MENINGO-ENCEPHALITIS *

MYCOTIC ANEURYSM DUE TO BRUCELLA MELITENSIS VAR. PORCINE

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Contributions to our knowledge of Malta fever have been numerous since the discovery of the etiological organism by Bruce [1] in 1887. A search of the voluminous literature on this subject reveals quite frequently most of the complications and sequelae of a long-continued intravascular infection. Meningeal infection with Brucella organisms is an exceptional observation in the history of the disease. The localization of *Brucella melitensis var. caprine*† in the meninges, as far as we are aware, has been conclusively proved only on three occasions. Hughes,[2] in his thorough study and review of the subject, mentions a patient who, after forty-five days of fever, had been afebrile for fifty-seven days, when symptoms of cerebral irritation appeared. *Brucella melitensis var. caprine* was isolated from the meninges postmortem, fifteen days after the onset of the cerebral symptoms. Lemaire [3] made a complete study of a non-fatal case in which he pointed out the similarity of melitensis meningitis and tuberculous meningitis. He either failed to locate the report by Hughes, or he did not accept it as a case of melitensis meningitis, because he believed that his was the first case of meningitis reported in which *Brucella melitensis var. caprine* was the causative organism. Desage and coworkers,[4] having seen Lemaire's report, were in a position to make a diagnosis of melitensis meningitis on a patient who, after a number of consultations, had been given up to die, supposedly of tuberculous meningitis. Magnani [5] reported a series of observations on a possible case of melitensis meningitis. Roger [6,7] contributed nine clinical cases, six of his own and three from a text by Cantaloube, of probable infection of the meninges with the meli-

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† Because of geographic distribution of the cases, it is assumed that the organisms were from caprine sources.

tensis organism. The diagnosis in each case was dependent on clinical observation and a positive agglutination test. No organism was isolated.

After Evans,[8] in 1918, emphasized the close laboratory similarity between the causative organism of Malta fever and the organism responsible for contagious abortion, the possibility of human infection with the latter organism was promptly raised by Evans, Huddleson and other investigators. Soon authentic reports of human cases of infection with the *Brucella melitensis var. abortus* began to make their appearance. The differentiation of the Brucella group of organisms by the bacteriostatic dye method of Huddleson [9, 10] has clearly shown that *Brucella melitensis*, both porcine and bovine varieties, are pathogenic for man. The literature on human infection with these organisms has become more voluminous than that in which the original caprine variety of organism was implicated. The course of the disease, as well as the complications and sequelae, is similar even to the infrequency of meningitis. A review of the literature from 1918, the time the similarity was noted, to the present time has revealed only a single case due to the porcine organism, the pathology of which we propose to make the basis of this contribution. The clinical aspects of the case have been reported, in part, by Sanders.[11] No other instance of meningitis due to the bovine variety of organism has been found in the literature.

Report of Case

Clinical History: D. Y. (F-8521), a white, male, printer, 24 years old, entered the University Hospital on Oct. 10, 1931, and died on Nov. 3, 1931. He had been ill since Dec. 24, 1930. At that time, his right foot began to tingle and became numb. These sensations extended throughout the half of the body, even to the point of numbness of half of the tongue. He also developed aphasia. This attack lasted about thirty minutes. Following the first fifteen minutes of the numbness, a severe headache began in the temple and suboccipital regions, which lasted several hours. A number of similar attacks occurred later, except that they were initiated in an extremity other than the right leg. According to the mother, there had been four attacks of delirium. The patient was unable to recall anything about any of them. The first occurred in March, 1931, and lasted two hours. Lumbar puncture quite readily relieved his difficulties. He was admitted to Johns Hopkins Hospital the latter part of March as a brain tumor suspect, but no tumor could be located. However, evidence of intracranial irritation was present, and he was discharged. His illness was diagnosed encephalitis, or a low-grade meningitis. Two weeks after discharge, an organism of the Brucella group was isolated from the spinal fluid which had been obtained while the patient was in the hospital. Evidence of intracranial irritation had been

demonstrated by Doctor Sanders.[11] He found what he believed were meningococci, and the patient received antimeningococcic therapy. After the patient's return home, he was treated with vaccine prepared from an autogenous and stock strain of the Brucella organism, with what appeared to be quite a satisfactory result. Trouble with his eyes (diplopia) when looking to either side, ears (some impairment of hearing and throbbing in his ears), and headaches had, however, not entirely disappeared and lumbar puncture was at times necessary for relief. On Sept. 30, 1931, he became nauseated, vomited, and for two days had a temperature of 105° F. A low-grade fever had persisted since that time. Physical examination on admission to the University Hospital Oct. 7, 1931, disclosed nothing abnormal, except for prominence of the eyes, a 20 pound loss of weight, and a somewhat unsteady gait.

Subsequent Course: On October 25, there was a moderate occipital headache, and a lumbar puncture was done to relieve it. The patient became faint and had a convulsion. The pupils were dilated and fixed. There were two similar convulsions at 3.53 and 3.57 P.M., respectively. The fluid obtained at 4.00 P.M. was bloody. At 5.00 P.M. he was crying and tossing about. At 6.10 P.M. another convulsion occurred. The next morning at 2.10 A.M. he became stuporous and had deep, difficult respirations at the rate of 32 per minute. The pulse rate was 120. On October 27, definite choked discs and retinal hemorrhages were observed. On October 28, he was conscious and oriented, but weak. There was a dull ache in the back of the neck and he felt stiff all over. On the same day he was smoking and answered questions quickly and accurately. He complained of a stiff neck and of an occipital and suboccipital headache. On October 29, at 4.00 A.M., the pulse became imperceptible. Respirations were deep and sighing. The pulse returned shortly afterward at a rate of 120. On November 1, the head was retracted and the neck was stiff. The patient died suddenly on Nov. 3, 1931, at 7.40 A.M.

Laboratory Data:

Bacteriology: On March 20, 1931, Gram-negative organisms were found in the spinal fluid, which were interpreted as meningococci. A few days later a culture of the fluid examined at Johns Hopkins Hospital yielded a melitensis organism. On May 7, 1931, a *Brucella melitensis var. porcine* was isolated from the spinal fluid. On Oct. 26, 1931, five drops of uncentrifugalized spinal fluid on culture yielded no growth, while five drops of centrifugalized sediment yielded only seventeen colonies, which, when typed by Huddleson's bacteriostatic dye method, were proved to be *Brucella melitensis var. porcine.* On November 2, a similar organism was isolated from the spinal fluid. The fluid from the puncture on Oct. 26, 1931, was inoculated into two guinea pigs ("A" and "B"). The "B" pig was killed and autopsied after six weeks. Enlarged suppurating glands were found in the groin, the spleen was twice the normal size, and areas of necrosis were found in the liver and spleen. Organisms isolated from the lesions of this guinea pig proved to be *Brucella melitensis var. porcine.* The other pig, "A," was permitted to live and remain under observation.

Serology: On July 7, 1931, the patient's serum agglutinated the organism isolated from the spinal fluid, as well as a stock strain of Brucella in 1:160 dilution. On Oct. 22, 1931, the patient's serum agglutinated the stock strain of Brucella in 1:20 dilution, and the autogenous strain in 1:40 dilution. The spinal fluid agglutinated the stock strain in 1:5 dilution, and the autogenous strain in 1:10 dilution. The organism in the spinal fluid was agglutinated by known Brucella serum in a dilution of 1:1280. Guinea pigs "A" and "B" were bled on

December 15, and their sera agglutinated the Brucella organism in 1:1280 and 1:5120 dilutions, respectively. It was known before inoculation that their sera contained no agglutinins for the Brucella group.

Blood: The white blood cells varied from 9,200 to 15,900. There were 87 polymorphonuclear leucocytes, 10 lymphoid cells, and 3 large mononuclear cells.

Urine: There was nothing abnormal about the urine.

Spinal Fluid: The spinal fluid pressure was 52. On March 20, 1931, the fluid contained 300 cells, 36 per cent of which were lymphocytes. On May 7, 1931, there were 271 cells, only 12 per cent of which were polymorphonuclear leucocytes. Fluid obtained between Oct. 7, 1931, and time of the patient's death was markedly bloody in each instance. This bloody spinal fluid contained no reducing substace.

Postmortem Examination

The spleen weighed 175 gm. With the exception of three small hemorrhages in the visceral pericardium, and obvious emaciation, the gross findings were confined to the central nervous system.

Liquid and clotted blood filled the subarachnoidal space at the base of the brain from the optic chiasma to the brain stem, inclusive. Hemorrhage completely surrounded the brain stem and was continuous with the blood clot which filled the cisterna magna, fourth ventricle, aqueduct of Sylvius, and third ventricle. Except for accumulations of blood covering both gyri and sulci over the occipital lobes, left Sylvian fissure and the tip of the left temporal lobe, the hemorrhage in the subarachnoidal space of the cerebral hemispheres was in the sulci. The leptomeninges of the anterior and central portions of both superior surfaces of the cerebral hemispheres contained a number of grayish white "tubercles." Most of these were found definitely clustered along vessels. Blood, which filled the entire spinal subarachnoidal space, obscured all evidences of a meningitis.

After the brain was fixed in 10 per cent formalin, the cerebral and cerebellar peduncles were severed so that the pons, medulla and fourth ventricle were obtained in one piece. This was sectioned coronally without disturbing the subarachnoid hemorrhage. An aneurysm which measured 9 by 6 by 6 mm. arose from the dorsal surface of the proximal portion of the basilar artery. The major portion of the sac lay superior to its point of attachment to the basilar artery. A short pedicle, containing a channel 1 mm. in diameter, connected the lumina of the sac and artery. The aneurysm, the basilar artery and the vertebral arteries, all lay embedded in blood. Examination of the cerebral hemisphere revealed somewhat dilated lateral ventricles and a granular ependyma. A small amount of

blood was present in the tips of the ventricular horns. A firm, laminated blood clot completely filled the third ventricle.

Histological Examination

Histological examination of the viscera reveals considerable amounts of phagocytosed hemosiderin in the lungs and a few small focal areas of necrosis in the liver.

The nervous system presents changes due to a mild injurious agent. Both the pia and the arachnoid show various degrees of thickening, due largely to an inflammatory cell infiltration and a connective tissue proliferation. The inflammatory cells are largely lymphocytes and plasma cells, with a moderate number of large mononuclear cells. A few polymorphonuclear leucocytes are noted. Serial sections of several of the meningeal "tubercles" reveal that they are composed of irregular masses of hyalinized connective tissue, moderately infiltrated with chronic inflammatory cells. In one area, where the inflammatory cell infiltration is especially marked, necrotic tissue is present in which polymorphonuclear leucocytes are noted. In another similar area, the central portion is composed of large mononuclear cells surrounded by a dense collar of lymphocytes. Newly formed blood vessels are present in many of these inflammatory cell collections. It appears that these areas represent various stages in the formation of a "tubercle," from necrosis to connective tissue hyalinization.

Most of the meningeal vessels show a thickened adventitia, heavily infiltrated with inflammatory cells. There are all gradations between a thick collar of lymphocytes, in which very little adventitia is recognizable, to a thick collar of adventitial connective tissue heavily infiltrated with inflammatory cells. Several of the brain stem vessels show a partial replacement of the media by connective tissue with marked subintimal connective tissue proliferation. Inflammatory cells are present throughout the entire thickness of the wall in these instances. Where branches of the meningeal vessels pierce the cortex, a perivascular collar of inflammatory cells accompanies the vessels. Many of the cortical and subependymal vessels show perivascular collections of lymphocytes. This phenomenon is virtually confined to these two areas of brain substance. There are two small areas of softening in the brain stem. One submeningeal area shows vacuolization of cells, edema,

phagocytosed hemosiderin, inflammatory cell infiltration and snarled glia. The other, located 2 mm. from the meninges, is a more recent lesion composed mostly of large mononuclear cells, lymphocytes and cellular débris. A hyaline thrombus is noted in a small vessel.

The ependyma is irregular, due to rounded elevations and crypt-like depressions. Proliferation of ependymal cells, especially over the elevations, is noted. In some areas complete replacement of the ependyma by inflammatory cells and cellular débris is present. There is a small subependymal area of focal necrosis.

Inflammatory cells are present in the perineureii of the nerve roots. The central portion of one nerve funiculus is hydropic and the periphery shows condensation of nerve fibers, some of which are swollen.

Discussion

The spinal fluid is the important consideration in the study of melitensis meningitis. Lemaire made much of the increase of sugar in the spinal fluid. Desage and coworkers found opposite results. All are agreed that a mononuclear pleocytosis of the spinal fluid, the number of cells being frequently below 100 per cmm., is a very important consideration in the study of the spinal fluid of these cases. This has held true in our case, with the exception of the possibility of a polymorphonuclear preponderance early in the disease. The information on the counts of proved cases is tabulated below.

Author	Cells per cc.	Polymorphonuclear leucocytes	Mononuclear cells	Large mononuclear leucocytes	Small mononuclear leucocytes	Lymphocytes
		per cent	*per cent*	*per cent*	*per cent*	*per cent*
3	25	..	100	..	..	100
3	225	..	100	..	..	100
3	180	2	98	..	..	98
4	50	16	84	43	27	14
4	60	12	88	32	38	18
11	300	64	36	..	..	36
11	70	..	..	..	..	..
11	271	12	88	..	..	..

The central nervous system involvement may be the first and only clinical manifestation of the disease. Of the proved and probable cases, eleven were preceded by the septicemia symptoms characteristic of Malta fever; in three the disease was manifested only by a

meningeal irritation. The central nervous system involvement as the initial phenomenon of the disease renders the spinal fluid study extremely important. The blood may contain no agglutinins and the association of a meningitis with Malta fever may be overlooked. But the finding of the organism in the spinal fluid, the testing of its pathogenicity on guinea pigs, and the differentiation of the organism according to the bacteriostatic dye method of Huddleson, which constitute the only way to make certain a diagnosis, may be regularly accomplished. In no individual case is it safe to assume that a patient is suffering from Malta fever or melitensis meningitis on the basis of an agglutination titer alone. Many people have serum agglutinins for the Brucella group, with no symptoms. Here, as in other conditions, the agglutination reaction may lead one to an incorrect diagnosis, with disastrous results. We are too prone these days to accept an agglutination result as the determining factor in the diagnosis of the current illness. No procedure is comparable in trustworthiness to the isolation and identification of the organism, when this is possible. The isolation of the organism is relatively simple in melitensis meningitis if we keep in mind the fact that only a few organisms are present in a cubic centimeter of spinal fluid. It is general experience that the use of 10 cc. of inoculum has regularly yielded positive results. Our only failure in obtaining the organism was accounted for by too meager an inoculation. Desage and coworkers, and Lemaire, strongly emphasize this point.

The headache, the diplopia, the transitory paralyses, and the throbbing in the ears are outstanding in the course of the disease. Convulsions may occur. Desage used X-ray therapy successfully to relieve a paraplegia which he believed was due to adhesions of the spinal cord. Recovery was rapid following this therapy. The case report by Hughes mentions congestion as the only morbid anatomical change in the central nervous system. Our case showed no pathology which would cause a paraplegia, as Desage assumed. Other untreated cases, as well as our own, recovered from these paralyses equally as satisfactorily as the case described by Desage. It is conceivable that the encephalitis, and particularly the edema of nerves with swelling of nerve fibers, as evidenced in our case, might lead to the evanescent symptoms observed in this disease.

Any organism may be localized in the pia-arachnoid or in the larger vessels at the base of the brain for a long period of time. By

the feeding of a limited number of organisms, or by the diffusion of the bacterial poisons from the localized process into the spinal fluid, or by both mechanisms, a chronic meningitis may be produced. These are atypical cases, but must be kept in mind. Here we consider diffuse infection of the meninges by widespread distribution of the causative organism in the subarachnoidal space, which results in a chronic meningitis. The *Hemophilus influenza* group of organisms, the *Treponema pallidum*, the *Mycobacterium tuberculosis*, and the *Torula histolytica* are well known as causative agents in chronic meningitis. To this group we must now add meningitis due to the organism of the Brucella group. Involvement of the meninges by members of the *Hemophilus influenza* group is easily recognized. The symptoms are more acute than in any of the other four types mentioned. The inflammatory cell in the spinal fluid is the polymorphonuclear leucocyte. The course of the disease is usually that of a basilar meningitis of about a month's duration before resulting in death. The tuberculous meningitis is very similar, except that evidence of meningeal irritation is not so severe. Headache is sometimes a distressing symptom. The course of the disease averages about six weeks in duration, and usually terminates in death. Mononuclear cells usually predominate in the pleocytosis of the spinal fluid, but counts of 75 per cent of polymorphonuclear leucocytes may obtain in tuberculous meningitis. Torula infection is accompanied by severe headaches and at times marked evidence of intracranial pressure. So marked is the intracranial pressure that the slightly stiff neck and pleocytosis of the spinal fluid are disregarded, and brain tumor is erroneously diagnosed. The cells in the spinal fluid are chiefly mononuclears and the yeast-like organisms may be mistaken for cells in the fluid, unless one is on guard. Torula meningitis proves fatal in about six months. The symptoms of syphilitic meningitis and melitensis meningitis are frequently nothing more than a severe headache. Both diseases tend to recover. The melitensis meningitis is associated with startling, but evanescent, central nervous system symptoms such as hemiplegia, paraplegia, aphasia, diplopia and so on. There is a mononuclear increase in the spinal fluid in both instances, which may rise to several hundred cells. It is hardly worth while to go more extensively into the clinical differentiation of these conditions. Enough has been said for an intelligent approach to a definitive diagnosis through an accurate study of

the blood, and particularly of the spinal fluid, from an immunological and bacteriological standpoint.

Summary and Conclusions

1. A case of melitensis meningo-encephalitis is reported, with a review of the related literature.

2. A mycotic aneurysm due to *Brucella melitensis var. porcine* was the immediate cause of death.

3. According to the literature and in our own case as well, isolation of the organism from the spinal fluid is relatively simple, if approximately 10 cc. of inoculum is used.

4. Headache and evanescent paralyses are important central nervous system manifestations, and mononuclear pleocytosis is an outstanding feature of the spinal fluid.

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DESCRIPTION OF PLATES

PLATE 77

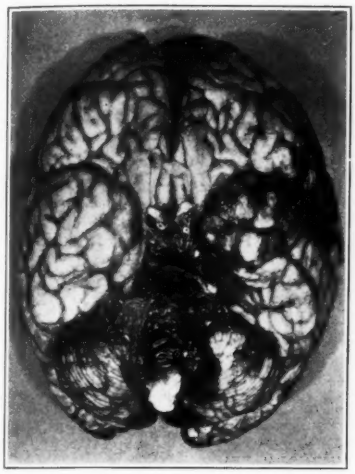
FIG. 1. Photograph of the ventral surface of the brain. Note the subarachnoid hemorrhage, especially over the base. The brain stem is completely encircled with blood. The basilar artery is not visible.

FIG. 2. Drawing of the superior cerebral surfaces. Note the clusters of "tubercles" located largely along vessels in the sulci.

FIG. 3. Photograph of a coronal section through the pons and fourth ventricle. Note the basilar artery and its aneurysmal sac embedded in blood clot. The fourth ventricle is filled with blood clot.

FIG. 4. Same as Fig. 3, after removal of fourth ventricle blood clot. Note the blood-stained ependyma. (Arrow 1 indicates basilar artery; Arrow 2 indicates aneurysm.)

FIG. 5. Photograph of coronal section through pons and fourth ventricle superior to Fig. 3. Note the superior extension (2) of the sac between the artery (1) and the pons.



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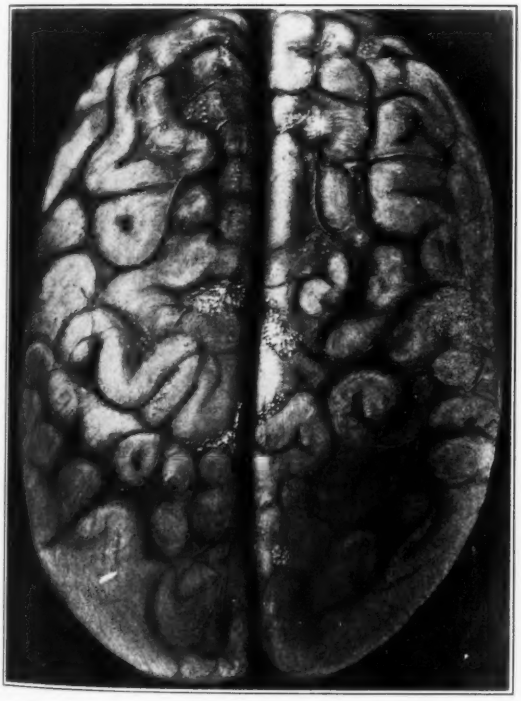

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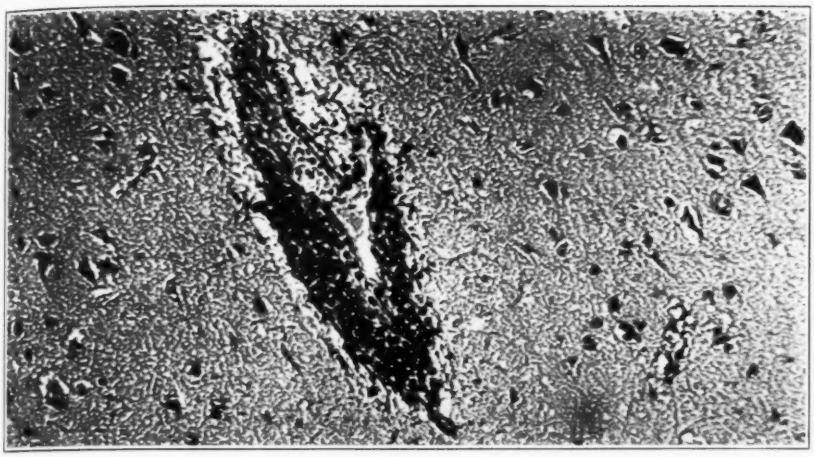
PLATE 78

FIG. 6. Photomicrograph of cerebral cortex. Note the dense perivascular lymphocytic infiltration. × 200.

FIG. 7. Photomicrograph of meninges and submeningeal area of necrosis of the brain stem. Note the vacuolization and glial replacement. Large "spider" cells are present. The pia is markedly thickened and heavily infiltrated with inflammatory cells. × 200.

FIG. 8. Photomicrograph of area of necrosis in brain stem. Note the large numbers of macrophages in the area of tissue liquefaction. × 200.



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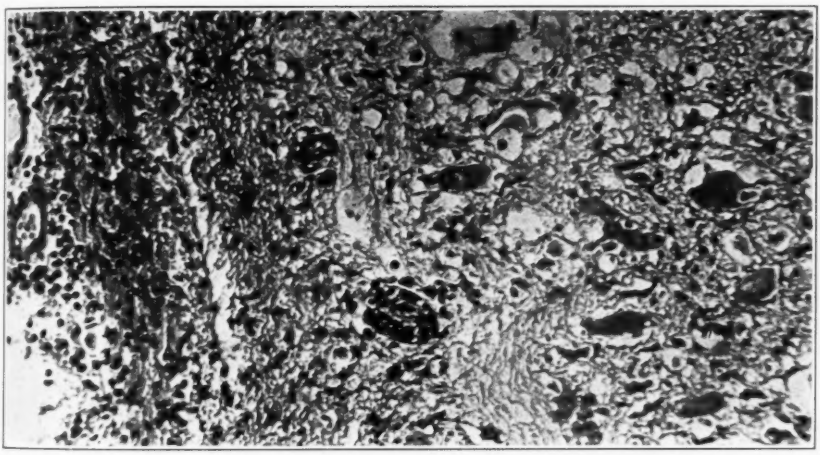

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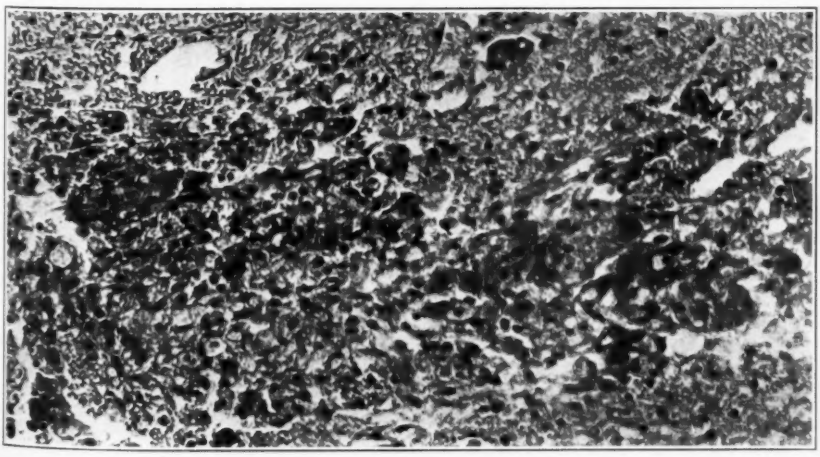

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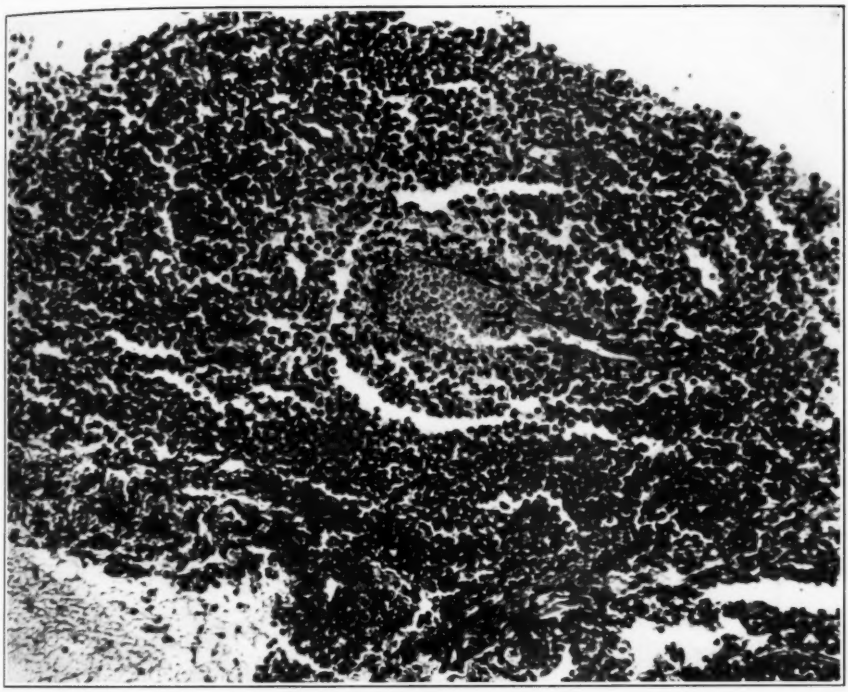
PLATE 79

FIG. 9. Photomicrograph of meningeal vessel showing a dense collar of lymphocytes. × 200.

FIG. 10. Photomicrograph of a small brain stem artery. Note the increased adventitial connective tissue heavily infiltrated with inflammatory cells and the marked destruction of the media with connective tissue replacement. Definite endarteritis is present. × 200.



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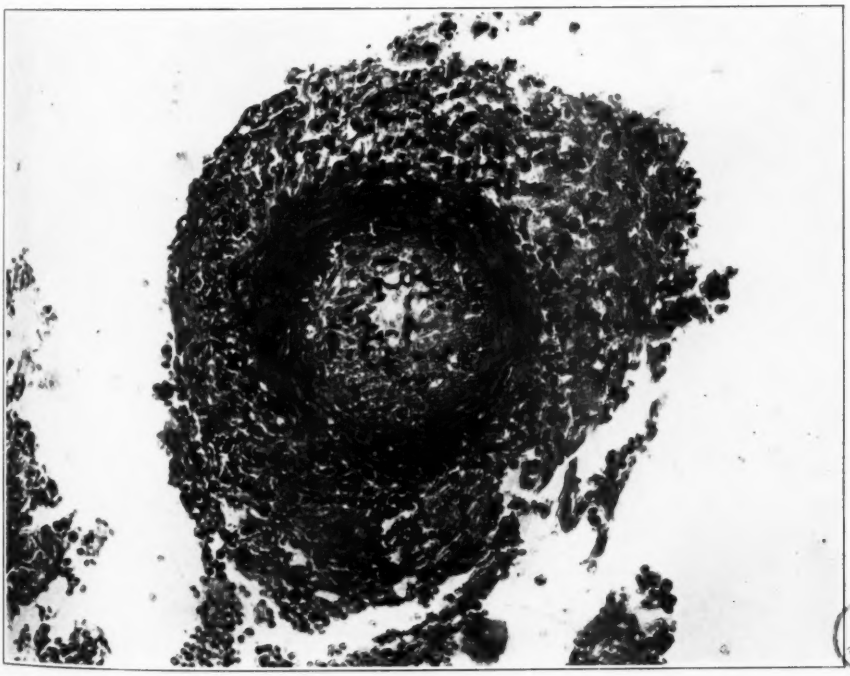

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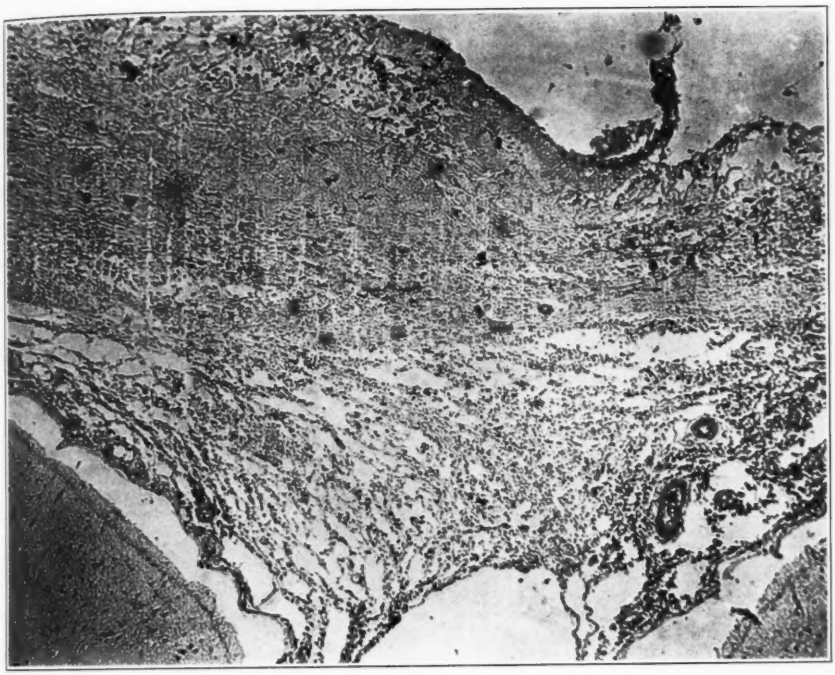
Plate 80

Fig. 11. Photomicrograph of the leptomeninges through a "tubercle" area. Note the marked thickening, inflammatory cell infiltration, connective tissue proliferation, the somewhat acellular hyaline area representing the tubercle, and the pia-arachnoid fusion. × 55.

Fig. 12. Photomicrograph of a funiculus of a nerve root. Note the central hydropic area with a peripheral condensation of fibers. × 200.



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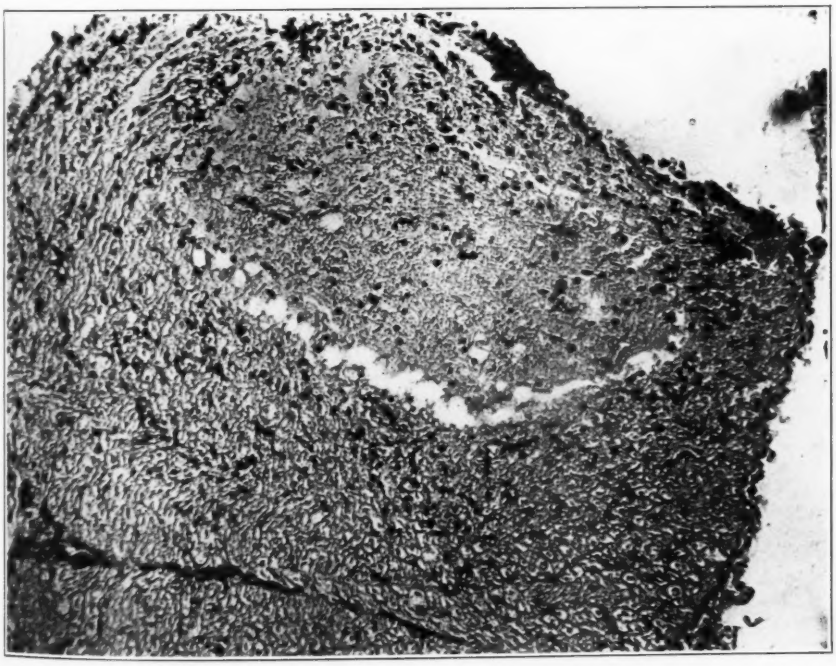

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AN INSTANCE OF ADAMANTINOMA OF THE JAW WITH METASTASES TO THE RIGHT LUNG*

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Since Guzack [1] in 1826 described the first case of cystic tumor of the lower jaw,† and Falkson [2] in 1879 gave the first full account of this condition, at least 130 cases of adamantinoma have been recorded.[3-20‡] Adamantinomas are tumors probably arising from the so-called "paradental epithelial débris," first described by Malassez.[21] The enamel organ develops by a downward growth of the gingival epithelium. All of the epithelium of the enamel organ, except its internal layer, undergoes atrophy and is absorbed. Occasionally these cells persist and it is believed that they are the histogenetic precursors of adamantinomas. The structure of the adamantinoma closely resembles the embryonal enamel organ.

Most investigators consider the adamantinoma a benign tumor.[22] It may, however, undergo malignant transformation, and where this occurs metastases having the histological structure of the malignant growth have been reported (Aschoff,[23] Ewing,[24] Kaufmann,[25] Heath,[26] Krompecher,[27] and others). Such malignant transformation develops usually after several local recurrences, following repeated excisions. From an analysis of the literature it is apparent that metastases from an adamantinoma are extremely uncommon. Eve [28] in 1883 described an unusual instance of a cystic tumor of the lower jaw of thirteen weeks' duration in a woman 60 years of age, who died of postoperative bronchopneumonia. Metastases to the lumbar lymph nodes were noted. Simmons [29] in 1927 reported two cases of adamantinoma with metastases. In one instance the metastases were in the regional lymph nodes, appearing fourteen years after the onset of the disease. In the second instance metastases were present in the glands of the neck and in the lungs. In both instances the patients

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† Sculter, cited by Albarran, J., *Rev. de chir.*, 1888, **8**, 429, is said to have described cysts of the jaw in 1654.

‡ Coryllos (ref. 3), gives a complete bibliography of the literature on this subject up to the year 1910.

had undergone operations for resection of the primary tumor. Unfortunately Simmons does not describe the histological structure of the nodules in the lungs. In the instance reported by Ewing [24] of an adamantinoma with metastases to the lung, the histological structure of the metastatic deposits was that of a malignant growth.

The following instance of an adamantinoma is reported because of the unusual metastatic lesion in the lung.

Case Report

An adult of 38 years was admitted to Montefiore Hospital on Sept. 3, 1930, with the chief complaint of a productive cough. Twenty-one years prior to the present admission, he first noted a lump in the right upper jaw. At that time excision of the tumor was attempted and five subsequent operations were performed, due to recurrence of the local lesion. In 1925 a small, soft, reddish tumor of the right upper jaw in the scar of a previous operation was removed at the Haggard Clinic in Nashville, Tenn. The area was cauterized and radium needles were implanted in the surrounding tissues. Pathological examination at that time showed the tumor to be an adamantinoma. A few months later a radical excision was performed. At the time of the operation the antrum was filled with a brain-like material which penetrated into the nasal cavity and involved the septum. Intensive radium treatment was given and the local condition healed. For a period of five years following this operation there was no evidence of recurrence locally. Two years ago, however, after an attack of "dry pleurisy," which confined the patient to bed for three weeks, he developed a productive cough with occasional blood-streaked sputum. About a year ago he complained of progressive weakness, anorexia, marked loss of weight and pain in the right hip. An X-ray of the chest taken at the Lebanon Hospital revealed a dense mass in the lower lobe of the right lung, extending from the sixth rib to the diaphragm and obscuring the right half of the latter. In the base of the left lung a circumscribed, moderately dense nodule the size of a large marble was also noted. Nothing abnormal was revealed in the X-rays of the right hip, pelvis and vertebral column. He was transferred to Bellevue Hospital where he received X-ray therapy for the lung condition.

At the time of admission to Montefiore Hospital, examination of the patient revealed a transverse and vertical scar on the right cheek. There was evidence of a partial resection of the hard palate and the right upper jaw, with a fairly large cavity in the roof of the mouth on the right side, measuring about 3 by 3 by 3 cm. opening into the nasopharynx. There was no evidence of recurrent growth. On examination of the chest there was a slight retraction of the fourth, fifth and sixth intercostal spaces over the right anterior wall. Expansion was slightly limited on the right side. Vocal fremitus was increased anteriorly from the third intercostal space downward and markedly diminished from the level of the eighth dorsal vertebra to the base. There was flatness posteriorly from the apex of the axilla to the seventh dorsal vertebra. Posteriorly the breath sounds were entirely absent below the seventh dorsal vertebra. Examination of the rest of the body revealed no abnormalities.

Nine months after admission the patient developed a septic temperature and signs of an empyema on the right side. A thoracotomy was performed and three

subpleural abscess cavities were drained. Following this his temperature dropped to normal. On histological examination of the tissue removed at operation a diagnosis of metastatic adamantinoma was made. Three months later he had a hemoptysis of 5 oz. of bright blood and continued to have blood-streaked sputum. A bronchoscopic examination, which was performed at that time, revealed a growth blocking the bronchus leading to the right lower lobe, from which bright red blood was oozing. Section from the tumor revealed the structure of an adamantinoma. Two days later he developed chills and a septic temperature, and for the first time a systolic and diastolic murmur were heard over the apex of the heart. There was no evidence of cardiac enlargement. An acneiform eruption then appeared over the chest and back. A culture of *Streptococcus viridans* was isolated from the blood stream. The patient became irrational and died.

Laboratory data showed no important findings other than the positive blood culture. Roentgenological examination of the maxillae and mandibles revealed no gross pathological changes other than those caused by the operative excision of the right upper maxilla. The mass in the right lung decreased slightly in size following a course of radiotherapy but subsequently again increased in size. The small nodule in the left base, after slightly increasing in size, completely disappeared. Roentgenological examination of the skull and skeletal system revealed no abnormalities.

Autopsy Report

Anatomical Diagnoses: Adamantinoma of the right upper jaw (postoperative) with metastases to the lower lobe of the right lung; polypoid thrombus attached to the auricular surface of the mitral valve with perforation of the leaflet; *Streptococcus viridans* septicemia with localization of the streptococci on the thrombus; splenomegaly; chronic passive congestion of the viscera; bronchopneumonia of the right lower lobe.

The body was that of a well developed, well nourished, adult white male about 165 cm. in length. There were a few petechiae in the inferior conjunctival sac of the right eye. There was anemia of the conjunctivae and lips, and cyanosis of the nail beds. There were no palpable lymph nodes in the neck, axilla or groin. Extending backward from the right angle of the mouth for a distance of about 2 inches there was a healed scar. The right cheek sagged inward as most of the maxilla and antrum wall had been removed from the right lateral incisors backward. The mucous membrane of the right cheek presented a healed scarred appearance. There was no evidence of ulceration. On opening the chest and abdomen, the dome of the diaphragm reached the third intercostal space on the right side and the fourth rib on the left. There was no fluid or air in either pleural

cavity. The right lung was closely adherent over the lower lobe posteriorly, laterally, and at the base.

The heart was not enlarged, and weighed 260 gm. The parietal pericardium adjacent to the lower lobe of the right lung was closely adherent to it. There was a moderate amount of epicardial fat which was well defined from the musculature. The myocardium was reddish brown in color and firm in consistence. The right auricle and ventricle presented no abnormalities. An occasional small, yellowish patch was seen through the endocardium in the right ventricle. The endocardium of the left auricle was somewhat opaque and grayish. Attached to the auricular surface of the aortic cusp of the mitral valve, by a broad base which measured 1.5 cm. in diameter, was a lobulated mass about the size of an olive. It had a somewhat smooth, greenish gray surface to which was adherent some dark red, clotted blood. The mass was fairly firm, somewhat elastic and quite friable. Most of the chordae tendineae of the aortic leaflet were markedly thickened and on the aortic surface of the aortic leaflet directly opposite the polypoid mass there was a punched out ulceration about 1 cm. in diameter. Its edge was fairly smooth and was covered in places by a small amount of grayish, friable material. The base of this ulcer around the periphery could be probed for a distance of about 8 to 10 mm. into the polypoid mass. In the central portion at a depth of 2 to 3 mm. a greenish gray mass similar to that of the polyp was present. This material was adherent to the lower margin of the ulceration. Clotted blood was removed from the ulcerated region. The tips of the papillary muscles were firm, and grayish white in appearance. There were many grayish streaks seen in the endocardium of the left ventricle.

The upper and middle lobes of the right lung were crepitant throughout. The pleura was smooth and glistening and presented no abnormalities. On section, the surface was reddish gray, mottled with anthracotic pigment with an occasional darker red area of congestion. A large amount of well aerated serous fluid and blood exuded on pressure. Bronchi and pulmonary vessels of these lobes presented no abnormalities.

The entire posterior part of the lower lobe was torn on removal, with marked destruction of the parenchyma. There was a large area in the upper anterior portion which was firm and non-crepitant. On section, the lung pattern was completely distorted and the alveolar

portions were markedly diminished in amount and obscured. The bronchi were dilated and very prominent. In the lower portion of the lobe they formed large bronchiectatic cavities with smooth-ribbed walls and with bands running through them. The whole bronchial tree, wherever it was intact, was plugged with a cast composed of fairly firm, somewhat friable, grayish white tumor tissue. In some areas this plug measured 2 to 2.5 cm. in diameter. Although for the most part this cast lay free in the bronchi, in some areas the walls of the bronchi seemed to be invaded. The cartilages of the larger bronchi were somewhat thickened in some areas and in others thinned out. There was an occasional large patch of the remaining alveolar portion which was completely replaced by tissue similar to that found in the bronchi. This tissue seemed to invade the bronchial wall and in places the mucosal surface was raised by irregular, grayish white patches. The upper anterior portion of this lobe was completely consolidated. On section the surface was yellowish gray and translucent, with areas of necrosis and many small cavities surrounded by reddish zones.

The left lung was similar to the upper and middle lobes of the right lung, with the exception of a small nodule found in the middle of the lower lobe. This nodule was about 1.5 cm. in size, well defined from the rest of the parenchyma, and seemed to be composed of firm yellowish material. There was a small amount of fibrosis around it.

The spleen weighed 220 gm. and measured 14.5 by 9 by 3.5 cm. The organ was enlarged, soft and somewhat flabby in consistence. The capsule was bluish gray in color and presented no abnormalities. On section the surface was purplish red in color with many irregular areas of hemorrhage and congestion. The corpuscles were indistinct but the trabeculae were quite prominent. The pulp scraped with ease on the edge of the knife.

There were no other abnormalities found in the rest of the viscera, other than chronic passive congestion.

Histological Examination

On microscopic examination the heart shows fragmentation of muscle fibers, cloudy swelling, small areas of perivascular edema and round cell infiltration, foci of cellular infiltration between muscle fibers composed of round cells and occasional polymorphonuclear

leukocytes. Occasionally in some areas the polymorphonuclear leukocytic infiltration predominates.

The thrombus on the auricular surface of the aortic leaflet of the mitral valve shows tissue composed of necrotic material. Large masses of bacteria and fibrin are present and the base of the polypoid mass contains very dense cellular connective tissue which is partly hyalinized. The tissue is markedly vascularized with small capillaries which are congested. There are numerous round cells and polymorphonuclear leukocytes.

Sections through portions of the lung uninvolved with tumor show extensive edema and congestion of the vessels. In some areas alveoli are filled with large mononuclear cells which contain brown pigment. Occasionally these cells are fused to form giant cells with nuclei arranged eccentrically.

An area of consolidation of the upper portion of the right lower lobe shows extensive fibrosis, atelectasis and atypical epithelial proliferation in some of the infundibula, and alveoli in the fibrotic areas. The wall of a bronchus shows very marked dilatation of the lumen (bronchiectasis), striking inflammation of the wall with extensive infiltration of round cells, polymorphonuclear leukocytes and newly formed blood vessels. One of the large blood vessels shows some thickening of the wall with adherent thrombotic material in the lumen. Areas of bronchopneumonic exudate are present.

Section through tumor of lung shows large irregular islands of tumor cells separated by dense fibrous connective tissue. These tumor masses have an outer layer composed of elongated cylindrical epithelium arranged in a vertical orientation to the surface. Occasionally there are two layers of cells of this type. The rest of the tumor masses are composed of spindle-shaped and round cells in a very loose meshwork of fine fibrillar connective tissue. The cytoplasm of the cells within the core of the nodules is scanty. An occasional fine process can be seen definitely radiating outward, communicating with similar processes in other cells (star-shaped cells). In the center of some of the islands within the core of the tumor mass the cells are arranged in a whorl resembling the beginning of epithelial pearl formation. An occasional small, cyst-like space is present within the tumor masses. There is no evidence of a malignant transformation. There is a striking similarity between the histological structure of this tumor tissue and that of the enamel organ of a four month fetus.

Other portions of lung where the tumor fills the bronchus and invades the surrounding tissue show that the tumor within the lumen of the bronchus is identical with that described above. In addition there are small areas of hemorrhage and necrosis. In other areas tumor is seen in the surrounding pulmonary tissue, invading the wall of the bronchus from within and encroaching on the cartilage within the bronchial wall. At the points where the tumor tissue invades the cartilage the tumor cells maintain their original adamantinomatous structure.

The nodule in the left lower lobe is composed of a very necrotic hyalinized material surrounded by cellular granulation tissue which is well vascularized. No evidence of tumor is present in the necrotic nodule. The surrounding lung tissue is congested and in places atelectatic and fibrotic.

The spleen shows evidence of marked congestion. The follicles are small, arterioles thickened. There are many cellular elements in the sinuses, some of which are plasma cells and round cells. An occasional erythrophagocyte is observed.

Discussion

From the review of the literature it is apparent that adamantinomas rarely metastasize. The presence of a large, secondary focus in the lung showing the histological structure of an apparently benign adamantinoma, in the instance reported in this communication is, therefore, unusually interesting.

The peculiar structure of the tumor in the lung was striking. The tumor filled the bronchial tree of the right lower lobe in a cast-like form and markedly distended the lumina of the bronchi. The bronchiectasis resulting from the inner pressure was extreme. The parenchyma, in places, and the pleura were extensively invaded. In view of this unusual manner of growth of the tumor it is suggested that tumor cells were aspirated from the primary focus in the jaw. In favor of this hypothesis are the following facts.

1. Such aspiration of tumor tissue was possible since the primary tumor in the upper jaw extended into the antrum and impinged on the nasopharynx. Furthermore, the patient had undergone several operations in which a general anesthetic had been administered.

2. The secondary tumor in the lung was present only in the right lower lobe. Jackson [30] found that aspirated foreign bodies lie most frequently in this site.

3. The growth of the tumor in the bronchial tree with the development of distention bronchiectasis further supports the theory of intrabronchial spread.

4. Both the gross and microscopic appearance of the metastasis closely resemble the primary benign growth in the jaw. Histologically, the section of the tumor in the lung is that of an ordinary adamantinoma.

5. There was no local lymph node involvement, and no metastases were found elsewhere in the body. This suggests some other method of spread of the secondary deposit than via the blood stream or lymphatics.

If the tumor was transplanted by aspiration it is necessary to assume that the tumor cells grew in the bronchial mucus secretion and in the mucosa. Histogenetically, adamantinoma cells arise from cells which are the precursors of enamel-forming tissue. While no similar or analogous instance of growth of tumor cells in such a tissue culture medium *in vivo* is known to the authors, it is probable that these cells are particularly hardy in their capacity to withstand adverse conditions.

Summary

An instance of adamantinoma of the jaw with metastases to the lung is reported. The bronchi of the lower lobe were markedly dilated and their lumina filled with a cast of the tumor tissue. In places the parenchyma of the lung was invaded. It is suggested that the tumor tissue was aspirated into the lung from the primary tumor, via the trachea and bronchial tree, and grew primarily within the lumina of the bronchi. No similar metastatic lesion of an adamantinoma in the lung was found reported in the literature.

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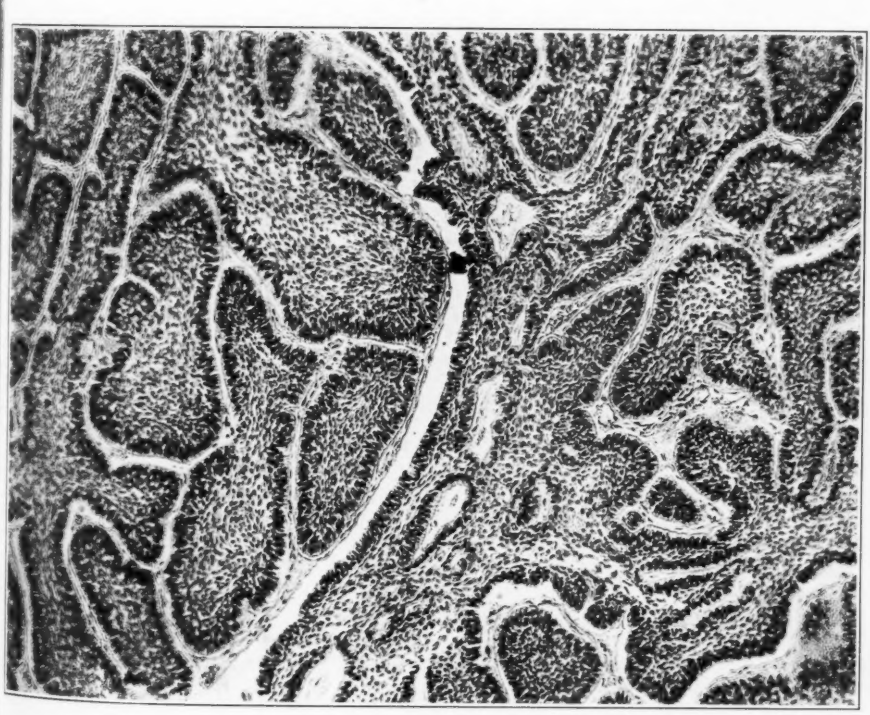
DESCRIPTION OF PLATES

PLATE 81

FIG. 1. Tumor cast in a bronchus. × 30.

FIG. 2. Section through tumor cast showing the histological appearance of adamantinoma. × 120.

1



2

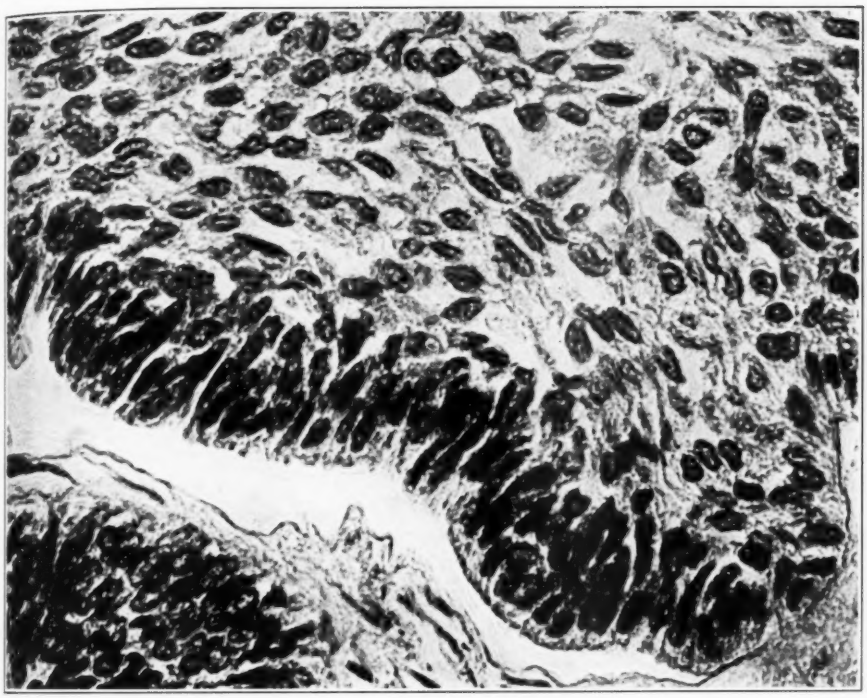
Vorzimer and Perla Adamantinoma of Jaw with Metastases to Lung

PLATE 82

FIG. 3. Same as Fig. 2. Higher magnification. × 440.

FIG. 4. Adamantinomatous tissue invading the cartilage of a bronchus.

FIG. 5. Nodule in left lung showing hyaline degeneration with connective tissue capsule. × 30.



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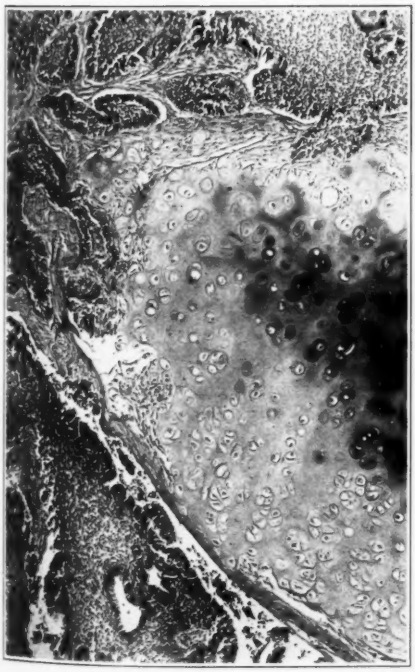

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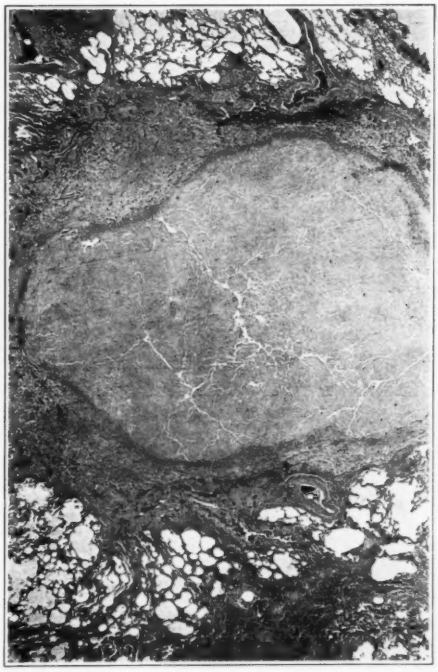

5

Adamantinoma of Jaw with Metastases to Lung

TRANSIENT PACHYMENIA OF THE INTIMA OF THE AORTA WITH REFERENCE TO JUVENILE ARTERIOSCLEROSIS *

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During recent years much interest has developed in the subject of juvenile arteriosclerosis, and, as a result of careful observation and study, the conclusion that arteriosclerosis occurs in children much more frequently than was formerly believed is being commonly accepted. Although the names of many different authors who have dealt more or less directly with this matter are mentioned by Zeek[1] in a recent review of the literature, little is to be found on the subject beyond the fundamental contributions of Thoma and those of Jores concerning developmental changes in the intima of the aorta after birth. Such changes evidently occur, for the majority of authors maintain that the intima in the newborn is formed by endothelium and the elastica interna alone. The excessive development of the subendothelial layer of the intima, however, can hardly be separated from the early arteriosclerotic changes in young subjects.

Thoma [2] has shown that the connective tissue layer of the intima develops after birth, and is a rather sparse structure below the level of the ductus arteriosus. Gradually, in the course of the first year, it begins to increase, and at 5 years a definite connective tissue layer is present in the descending and abdominal aorta. This occurs only in the portions of the vessel in which the so-called "Nabelblutbahn" previously existed. Thoma [3,4] states that the cessation of the placental circulation is responsible for a physiological hyperplasia of connective tissue in the intima. This hyperplasia results as a compensatory process and is referred to by him as "kompensatorische Intimawucherung." Thoma's [5] view, explaining the thickening of the intima by connective tissue as a result of a slowing of the blood stream, has not been universally accepted. Jores [6,7] considers the

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layer of connective tissue of the intima in children as a type of hyperplastic thickening.

More definite advance in our knowledge of arteriosclerosis will be made, in the opinion of Klotz, by a careful analysis of its very early stages, particularly those occurring in childhood. Indeed, by the twentieth year of life the picture generally is too complex to allow a proper appreciation of the real factors concerned in the pathology of this disease. Upon his suggestion I investigated the aortas of twenty children between the ages of 2 days and 10 years, having in mind the pathological changes previously reported in infectious diseases (Klotz,[8] Stumpf,[9] and Klotz and Manning[10]). The material was obtained, by the courtesy of Dr. I. H. Erb, from recent autopsies at the Hospital for Sick Children, Toronto, Canada. As the work progressed, it was found that developmental changes were the most interesting feature in such material, since there is so little about them in the literature, and since they were so striking in the group of children I examined.

Methods

In most cases the whole aorta was available. The material was fixed in 5 per cent formalin. The vessel was carefully handled when in the fresh state and was never washed in water or injured by rough usage. Five specimens from each case were examined. Portions were taken from the ascending aorta near the aortic valves, from the transverse aorta near the origin of the innominate artery, from the thoracic aorta between the fourth and fifth pair of intercostal arteries, and from the abdominal aorta above the origin of the common iliacs. As a rule the aorta was cut longitudinally before being fixed. In a few cases, the entire aorta was fixed before opening. This was done in order to avoid artefacts resulting from shrinkage, with consequent apparent thickening of the intima. In other cases, portions of the aorta were submitted to a considerable over-distention while being fixed, the ends of the vessel being tied to a lightly bent rubber tube, which was distended and maintained in a straight position by attaching it to a glass rod, and the whole was then immersed in formalin. The anterior and posterior parts of the vessel were always carefully determined before removing blocks for section. Complete transverse sections were obtained in most cases.

Frozen sections were employed, and the following stains were used on each specimen: Schultz' stain for demonstrating the mucoid

or chromotropic substance of the connective tissue; Sudan III-cresyl violet; Sudan III-cresyl violet-hematoxylin; and Sudan III-hematoxylin. Smith's method (Nile blue sulphate) and examination under the polarising microscope with the Nichols prism were also used for the identification of the fats. In a number of instances paraffin sections were studied for comparison. They were stained by hematoyxlin-eosin, Schultz' stain and Verhoeff's elastic tissue method.

Schultz' Stain for Vascular Mucous or Chromotropic Substance

Formalin fixation, paraffin or frozen sections. (1) Stain sections in 5 per cent aqueous solution of cresyl violet extra (Kresylechtviolett R extra) for 20 to 30 minutes. (2) Differentiate quickly in a very dilute aqueous solution of acetic acid (2 to 3 drops in 30 cc. of water) until no clouds of stain come from the sections. (3) Rinse in water. (4) Wash briefly in very dilute aqueous solution of ammonia. (5) Wash thoroughly in several changes of water. (6) Mount in levulose jelly.

The color will last for several weeks: nuclei violet, the chromatin appearing very well stained; vascular connective tissue in varying shades of bright purplish red to pale pink; collagen pale grayish blue or unstained; muscle tissue pale bluish; red blood corpuscles bluish or greenish; fibrin often bright blue; elastic tissue sometimes unstained in young subjects and later in varying shades of blue to bright cobalt blue. For the aorta of infants the most satisfactory procedure is to stain the frozen sections for 1 hour, immerse them briefly in dilute aqueous acetic acid and then wash them thoroughly in water. The elastic tissue stains pale greenish blue in this way.

Though non-specific, Schultz' stain is very useful for the study of the elastic tissue as well as the chromotropic substance in the aorta. It demonstrates the segments of the elastic membranes in which the specific elastic substance is already formed, while in those in which this substance is lacking, a metachromatic color reaction is obtained. Therefore, the less advanced the developmental stage of the elastic membranes are in childhood, the more they will appear as rose-red or colorless segments interposed between greenish blue and homogeneous ones.

A variant of this method is useful for showing the flocculation of the chromotropic material as well as fatty changes. (1) Stain frozen

sections in a concentrated solution of Sudan III in 70 per cent alcohol. (2) Dip in 70 per cent alcohol. (3) Wash in water. (4) Stain in 5 per cent aqueous solution of cresyl violet for 3 minutes. (5) Wash in water. (6) Stain in dilute Harris' hematoxylin for 1 to 3 minutes. (7) Wash in water. (8) Mount in levulose jelly (8 gm. levulose in 10 cc. water).

Observations

Case 259. Baby T., male, 2 days old. Autopsy 2½ hours postmortem. *Anatomical diagnoses:* Intracranial hemorrhage; laceration of tentorium cerebelli.

The intima throughout the aorta fails to show a subendothelial layer. In the thoracic aorta the elastica interna is formed by very irregular, short, homogeneous, bluish-stained segments (Fig. 1a) separated by narrow, tortuous, pink-stained portions. Its internal surface shows numerous processes simulating buds or sprouts (Fig. 1a). In the media the outlines of the central elastic membranes are not straight and regular (Fig. 1 b); the more external fibers are formed by wide, homogeneous, bluish segments alternating with others, pale pink or unstained ("tapeworm appearance" Fig. 1 c). In the abdominal aorta, however, the laminae of the midzone are quite continuous, straight and uniformly blue.

Case 251. R. M. G., female, 14 days old. Autopsy 4 hours postmortem. *Anatomical diagnoses:* Acute omphalitis; septicemia (*Streptococcus hemolyticus*); peritonitis; leptomeningitis.

The intima throughout the aorta is formed by endothelium and the elastica interna, the latter quite distinct in the abdominal aorta. Tested by Schultz' method the elastic membranes show a varying appearance at different levels. In the media of the ascending aorta they are formed by discontinuous, pale greenish, homogeneous segments embedded in a hyaline substance suggesting the formation of elastic fibers in an amorphous matrix. They simulate the early developmental structure, the elastic substance existing only in discontinuous plates. In the transverse aorta this appearance is less marked and is limited to the more internal or the more external elastic lamellae; the central ones are formed by continuous homogeneous strands (elastic substance) which run in parallel bands. In the thoracic aorta these features are less marked. Here, on its inner surface, the elastica interna presents numerous fine, oblique processes which stain like the elastic substance, while its external surface is regular. In the abdominal aorta the developmental characteristics are limited to the elastica interna, while the remaining elastic membranes appear uniformly greenish and show a regular arrangement in the media.

In the ascending aorta a marked perivascular infiltration by polymorphonuclear and endothelial leucocytes is noted around the vasa vasorum. Some of these inflammatory cells extend through the remaining portions of the vessel wall.

Case 253. K., female, 6 weeks old. Autopsy 5½ hours postmortem. *Anatomical diagnoses:* Empyema of cerebral ventricles; spina bifida; acute peritonitis; acute omphalitis.

In the ascending aorta the intima is very thin and formed by endothelium and elastica interna alone. In the transverse, thoracic and upper abdominal aorta the intima presents a continuous subendothelial layer that gradually becomes

thicker and forms sloping overgrowths. These are more marked at the transverse and upper abdominal portions than at the thoracic, and consist of fibrous connective tissue enclosing flattened and star-shaped fibroblasts as well as smooth muscle fibers. Large vacuolated cells, some of them containing fat droplets and presenting vacuolar degeneration and necrosis, are also demonstrable. In the abdominal aorta near the common iliacs a very thin subendothelial layer exists.

Fatty degeneration of the elastica interna is found in the abdominal aorta where this membrane is very distinct. Slight flocculation or mucoid degeneration of the chromotropic tissue, as well as perivascular infiltration around the vasa vasorum, are present in the ascending and transverse aorta. While in the transverse aorta almost all the elastic membranes possess discontinuous, greenish-stained segments (Schultz' stain), this aspect is less marked in the thoracic aorta and still less in the abdominal aorta. In the latter portions this discontinuity concerns chiefly the elastica interna.

Comment: In this case sloping overgrowths of the intima are found not only in the thoracic and abdominal aorta, but also in the transverse aorta as well. They are less marked in the thoracic segment than in the other parts. Definite degenerative changes in the intima represent a response to the infectious intoxications that existed practically from birth. This case illustrates well the difficulty of distinguishing between developmental and pathological changes in the aorta of infants. The irregular arrangement of the mononuclear and connective tissue cells, as well as the presence of intracellular and free fat, suggest a definite pathological change.

CASE 263. M. O., male, aged 7 weeks. Autopsy 2½ hours postmortem. *Anatomical diagnoses:* Marasmus; congestion of the abdominal viscera.

The subendothelial layer is found only in the abdominal aorta; it is lacking completely in the other segments. It is continuous and forms a quite marked sloping overgrowth 3 mm. above the origin of the common iliacs, being discontinuous just above the celiac axis (Fig. 2). A few cells containing fat droplets exist at the sloping overgrowth.

CASE 246. W. M. D., male, 2 months old. Autopsy 20¼ hours postmortem. *Anatomical diagnoses:* Otitis media; edema of brain.

The subendothelial fibrous layer of the intima is found only in the lower abdominal aorta. It is discontinuous, forming three different, rather small, sloping overgrowths, when a complete transverse section is examined. Slight perivascular infiltration around the vasa vasorum at the ascending aorta is the only pathological finding.

CASE 254. M. E., female, 2½ months old. *Anatomical diagnosis:* Bronchopneumonia (both lungs).

The subendothelial fibrous layer of the intima is continuous at the transverse, the thoracic and the abdominal aorta near the origin of the common iliacs, but discontinuous at the mouth of the left renal artery. At the posterior part of the vessel a very marked thickening of the subendothelial layer is found in the transverse, thoracic and abdominal aorta (Figs. 3, 4 and 5). The structure consists of young connective tissue, except in the transverse aorta. Fibroblasts containing anisotropic fat droplets, vacuolation of the connective substance, and fine extracellular fat droplets near the elastica interna are found in the sloping overgrowths in the abdominal aorta. The degenerative processes are slight and not found in other portions, being clearly limited to the sloping overgrowths. Chromotropic tissue is more evident in the inner half of the media. The elastica in-

terna is formed by homogeneous, bluish segments (Schultz' stain) separated from one another by narrow, tortuous, pink or colorless portions; numerous delicate processes were also seen on its inner surface.

CASE 1. D. R., male, 3½ months old. Autopsy 9 hours postmortem. *Anatomical diagnoses:* Nasopharyngitis; otitis media.

In the ascending aorta the intima presents no subendothelial layer. The latter appears continuous at the thoracic and lower abdominal aorta. At the upper abdominal aorta it is discontinuous, presenting a gradual thickening at the back part of the vessel, and forming a typical sloping overgrowth. The structure shows star-shaped fibroblasts resembling young connective tissue. Fatty degeneration of the lining endothelial cells and of fusiform cells in the subendothelial layer is found in the thoracic and abdominal aorta, being distinctly more marked at the sloping overgrowth.

CASE 265. C. B., female, aged 4 months. Autopsy 19 hours postmortem. *Anatomical diagnoses:* Acute enteritis, nasopharyngitis.

The subendothelial layer is lacking in the ascending and transverse aorta, existing and continuous at the thoracic aorta, and discontinuous in the abdominal aorta. The thickness of the intima is not uniform, being thin in the thoracic aorta and terminating in tapering ends at the abdominal aorta. Sloping overgrowths are present in those portions. Fatty changes are quite marked in the intima of the thoracic aorta. Cellular infiltration of the media and around the vasa vasorum is noted at the ascending aorta. The elastica interna presents a discontinuous appearance.

CASE 261. R. A., male, aged 5 months. Autopsy 14 hours postmortem. *Anatomical diagnosis:* Acute purulent leptomeningitis.

In the transverse aorta the intima does not show a subendothelial layer, while a sloping overgrowth is found in the thoracic portion. The latter appears thick and bulges a little above the normal level of the intima (Fig. 6 a). The thickness of the intima in this portion corresponds to a little less than half that of the media. The structure shows flattened cells, stellate or spherical in outline, many of them containing fat droplets and forming distinct fibrous lamellae. Less marked sloping overgrowths are noted at the abdominal aorta (Fig. 6 b and c); the subendothelial layer terminates in tapering ends in the specimen near the common iliacs.

Marked fatty degeneration and flocculation of the chromotropic tissue are seen in the intima at the sloping overgrowths, especially in the thoracic aorta. They do not coexist, however, in the same strata, as the fatty degeneration is more marked near and on the endothelium, while the mucoid degeneration is more intense in the deeper strata adjoining the elastica interna. Examination under the polariscope with the Nichols prism reveals anisotropic fat droplets.

Comment: A sloping overgrowth was definitely more marked at the thoracic than at the abdominal aorta, and more in the lower than in the upper abdominal aorta.

The study of sections from the thoracic aorta (Schultz' stain) suggests that the development is more advanced in the elastic membranes in the middle portion of the media than at the internal or external portions (Fig. 7).

It is curious to observe in this case the presence of pathological changes just at the developmental thickenings. This is true especially with regard to fatty changes; the more marked the thickening the more numerous are the cells containing fat droplets.

CASE 260. Y. F., female, aged 5 months. Autopsy 12 hours postmortem. *Anatomical diagnoses:* Septicemia; infected wounds of the skin; otitis media (*Streptococcus hemolyticus*).

A discontinuous subendothelial layer of connective tissue is found in the ascending and transverse aorta. In the remaining portions of the aorta this layer is continuous throughout the intima, forming a marked overgrowth in the thoracic aorta.

A few cells containing fat droplets and large vacuoles are seen in the intima, especially in the overgrowth of the thoracic aorta. Moreover, in that portion peculiar homogeneous, non-cellular, round masses, staining grayish blue with cresyl violet are lying among collagen fibrils. Marked flocculation of the chromotropic tissue is seen in the internal portions of the media of the transverse aorta.

CASE 240. K. H., female, aged 7 months. Autopsy 14 hours postmortem. *Anatomical diagnoses:* Acute bronchitis; double otitis media.

In the ascending aorta the intima is formed by the endothelium and elastic layer. The intima of the transverse aorta presents a well developed layer in which fibroblasts may be seen, while the elastica interna is distinguished with difficulty. In the thoracic aorta, the elastica interna is very distinct. The intima becomes much thickened at one point and then diminishes, so that a typical sloping overgrowth may be seen. It is formed by endothelium, a subendothelial or connective tissue layer and an elastic layer. In the latter, many smooth muscle fibers exist. The subendothelial layer contains branched connective tissue cells, more or less regularly arranged. The developmental and fatty changes simulate arteriosclerotic changes. In the abdominal aorta the intima is thinner, presenting a continuous subendothelial layer. No sloping overgrowth is formed in spite of a varying thickness of this layer.

Chromotropic connective tissue is more distinct in the internal half of the media. The elastica interna presents a very irregular inner surface. In the thoracic aorta it is formed of short, homogeneous segments, which probably correspond to islands of the elastic substance. They alternate with narrow, immature portions. The same appearance is found in the abdominal aorta, but the elastic segments are longer. The elastic lamellae of the media stain uniformly greenish blue, except some external ones, in which greenish segments alternate with pink ones.

In transverse paraffin sections stained by Verhoeff's method, the elastica interna is formed of small, irregular, deeply stained fragments. As these short fragments are quite distinct and separated from one another by narrow, colorless spaces, a rough and irregular surface is produced. Thoma [2] has described this appearance in the newborn as "ein eigenartige körniges Gefüge entsprechend einer Zusammensetzung aus dicht gedrängten, longitudinalen Faserbündeln und Fasernetzen."

Comment: A more or less advanced stage of arteriosclerosis is simulated by a developmental connective tissue plaque in the thoracic aorta of a child of 7 months, dying from an infectious process. Fatty changes are present in the overgrowth of the thoracic aorta. The fat is contained within cells, apparently fibroblasts, and appears to be of the nature of a cholesterol ester.

The intima of the abdominal aorta is of uniform thickness and presents a continuous subendothelial layer. If a sloping overgrowth has previously existed in this portion, it has now completely disappeared and the coat is distinctly thinner

and less cellular than in the thoracic aorta. Such peculiarities in the normal development of the intima are confusing, as they suggest pathological changes.

CASE 264. D. S., male, aged 7 months. Autopsy, 1½ hours postmortem. *Anatomical diagnoses:* Leptomeningitis; left otitis media (pneumococcus).

There was a well marked thickening of the subendothelial layer of the intima in the ascending and transverse portions of the aorta, while the thoracic aorta showed more diffuse thickening in the same layer. Occasionally small deposits of fat were also found in the connective tissue cells. The subendothelial structure formed separate bands in the abdominal aorta and shaded off to very thin structures in its lower portion.

Comment: It is interesting that although this child had suffered from an acute infectious process, the subendothelial layer of the aorta is distinctly less developed than in most of the children of this group. It would appear that these changes in the intima represent different stages in the development of the subendothelial layer.

CASE 255. M. L., female, aged 7½ months. Autopsy 12 hours postmortem. *Anatomical diagnoses:* Otitis media; sinus thrombosis (superior longitudinal sinus).

The continuous layer of subendothelial fibrous tissue rich in elastic fibers is present in the thoracic and abdominal aorta, while some fatty changes are localized in the ascending limb and the lower abdominal aorta.

Comment: Sloping overgrowths of the intima are absent in this infant of 7½ months, although they were quite marked in children of 4, 6 and 10 years of age.

CASE 244. T. M. R., female, aged 18 months. Autopsy 1 hour postmortem. *Anatomical diagnosis:* Diphtheria.

The subendothelial layer is undeveloped in the ascending and transverse aorta, but appears well formed in the thoracic aorta, forming a sloping overgrowth. In the upper abdominal aorta the subendothelial layer is disposed uniformly, while sloping overgrowth is again demonstrable near the origin of the common iliacs. Slight cellular infiltration around the vasa vasorum at the ascending and transverse aorta is the only pathological change of note.

CASE 248. M. G., female, aged 21 months. Autopsy 15 hours postmortem. *Anatomical diagnoses:* Lobar pneumonia; acute fibrinous pleurisy; otitis media.

In the thoracic and abdominal aorta the subendothelial layer is discontinuous, forming a typical, quite marked, sloping overgrowth near the mouth of the celiac axis (Fig. 8). The structure shows abundant connective tissue cells, some of them flattened and disposed in fibrous lamellae. A slight thickening of the intima is also seen in the lower abdominal aorta, above the origin of the common iliacs. No sloping overgrowth is found at the thoracic aorta. The elastica interna is formed by greenish segments (Schultz' stain), which alternate with pink or colorless portions.

CASE 252. R. M., male, aged 3 years. Autopsy 18 hours postmortem. *Anatomical diagnosis:* Diphtheria.

In this case of diphtheria, a slight perivascular infiltration around the vasa vasorum in the ascending aorta is almost the only pathological change demonstrable. A continuous subendothelial layer in the intima is found at the thoracic and abdominal aorta, while it is thin or lacking at the ascending aorta, and does not exist at the transverse aorta. A typical sloping overgrowth is detected only in the abdominal aorta near the common iliacs. One gains the impression that a sloping overgrowth is actually disappearing in the thoracic aorta, while another is demonstrable in the abdominal aorta near the bifurcation.

This case illustrates well the way in which the maturation or development of the elastic membranes proceeds. In the ascending and transverse aorta the elastica interna is not easily distinguished from the more internal elastic membranes of the media, and all of them present a segmented appearance (Schultz' stain), while in the thoracic and abdominal portions it is quite distinct.

CASE 241. P. C., male, aged 4 years. Autopsy 7¼ hours postmortem. *Anatomical diagnoses:* Osteomyelitis (left ilium); septicemia (*Staphylococcus aureus*).

The intima is very thin and formed only by endothelium and elastica interna from the ascending to the abdominal aorta. In the lower abdominal aorta immediately below the superior mesenteric, a discontinuous subendothelial layer is seen, which forms a typical sloping overgrowth at the back part of the aorta. A similar sloping overgrowth always posteriorly may be traced from the mouth of the right renal artery downward to a point 11 mm. above the origin of the common iliacs. The sloping overgrowth appears more marked as we trace downward and approach the origin of the common iliacs. The structure of the dorsal connective tissue plaque shows endothelium, young fibroblasts in a broad layer and some smooth muscle fibers near the elastica interna.

Islands of elastic substance in the elastica interna are seen clearly in the thoracic aorta (Schultz' stain), while the segments in which no elastic substance exists show a metachromatic reaction. Small pedunculated processes give an indented appearance to the internal surface of the elastica interna.

Comment: A dorsal connective tissue plaque limited to the abdominal aorta is continuous and can be followed upward from the origin of the common iliacs to the superior mesenteric artery, covering a distance of about 29 mm. of the aorta and always located at its posterior border. The subendothelial layer is no longer found above the orifice of the celiac axis. The dorsal connective tissue plaque, being quite marked in the lower abdominal aorta, becomes gradually attenuated and disappears entirely at the upper abdominal aorta.

CASE 262. M. T., female, aged 5 years. Autopsy 6 hours postmortem. *Anatomical diagnosis:* Acute fibrinopurulent peritonitis.

The subendothelial layer of the intima is well developed, continuous, and formed by flattened fibroblasts disposed in definite lamellae in the thoracic and abdominal aorta (Fig. 9). It has a more or less uniform thickness, no sloping overgrowth being detected in any portion. In the ascending and transverse aorta no subendothelial layer is found.

Comment: The absence of sloping overgrowths and the structure of the continuous subendothelial layer at the thoracic and abdominal aorta suggest a further stage in the development of the intima. Anisotropic fat droplets inside the lining endothelium and fibroblasts of the subendothelial layer, as well as extracellular fat droplets, are detected in the ascending and the abdominal aorta.

CASE 238. S. T., female, aged 6 years. Autopsy 12¾ hours postmortem. *Anatomical diagnosis:* Poliomyelitis.

In the ascending aorta the intima presents a fairly developed subendothelial and elastic layer. There are no fatty changes. Chromotropic connective tissue (Schultz' stain) is uniformly developed in the media, slightly increased in amount and flocculent in places. In the transverse aorta the intima shows a subendothelial and elastic layer with regularly arranged fibroblasts in the interspaces of elastic and collagen fibers. The elastica interna presents much longer blue-stained segments than those seen in younger infants. In the thoracic aorta the subendothelial layer is well developed, containing smooth muscle fibers in its deeper portion. The intima is of more or less uniform thickness, and rather thin.

In the abdominal aorta, the intima becomes progressively thicker, measuring 175 microns near the celiac axis. A typical sloping overgrowth is formed, similar to that found in Cases 241, 261 (Fig. 6), and 254 (Figs. 3, 4 and 5) children respectively 4 years, 5 months and 2½ months old. The structure shows numerous adult fibroblasts in regular arrangement.

Comment: The intima presents a continuous subendothelial layer throughout the vessel. This coat is thin and of uniform thickness in the ascending, transverse and thoracic aorta. While such distribution indicates a fairly advanced stage in the development of the intima, typical sloping overgrowths with all the characteristics described in Cases 254, 261 and 241, may be seen in the abdominal aorta. No fatty changes are noted; flocculation or mucous degeneration in the ascending aorta is the only pathological finding.

CASE 245. D. O., male, aged 10 years. Autopsy 3 hours postmortem. *Anatomical diagnoses:* Cerebral abscess (left hemisphere); acute purulent leptomeningitis; otitis media.

In the ascending aorta the intima is formed by endothelium and elastica interna only, the latter not being easy to distinguish from the other elastic membranes. In the transverse aorta a few stellate cells lying in a thin network of elastic fibrils are present. In the thoracic and abdominal aorta the intima shows a very distinct elastica interna and a continuous subendothelial layer. Its thickness is more or less uniform and distinctly thinner than in the aorta of infants 2 to 4 months old. Near the celiac axis, however, the intima very gradually becomes thicker, so that a cellular overgrowth is produced. Fatty changes appear focally at the mouths of the intercostal arteries. A small amount of intra- and extracellular fat is found in this limited portion of the intima. Mucous degeneration was very marked in the chromotropic tissue throughout the media in the asecnding and transverse aorta.

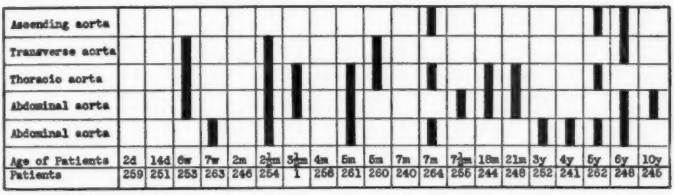
Comment: Only a slight sloping overgrowth is detected in the upper abdominal aorta. The intima is distinctly in an advanced stage of development in the thoracic and abdominal aorta, as compared with that in other children of this group. It is continuous, thin, fairly uniform in thickness, with fibroblasts disposed evenly and in collagenous lamellae. In the ascending and transverse aorta, however, no subendothelial layer exists. The infectious disease is probably responsible for the superficial fatty streaks at the mouths of the intercostal arteries and for the marked flocculation (mucous degeneration) of the chromotropic connective tissue in the ascending and transverse aorta.

DISCUSSION

Thickenings of the intima on the posterior part of the aorta are demonstrable with great constancy in specimens from a group of children of different ages. They correspond, in some respects, to what Thoma[4] has described as "kompensatorische Intimawucherung," but appear to represent only the normal development of the intima, and in particular, of its subendothelial layer. As a matter of fact, the developmental plaques are not seen by the naked eye, as they do not rise above the surface of the aorta. This feature is important, as it distinguishes them from the common pathological lesions.

Not less important is the microscopic aspect. Such developmental plaques, when complete transverse sections are examined, increase gradually in thickness on the inner side of the elastica interna (Figs. 2, 3 and 8), until a maximum is reached. Beyond this, they again become gradually attenuated. Sometimes the subendothelial layer disappears completely at the edges, so that the sloping overgrowth appears more marked. This justifies the term "sloping overgrowth" of the intima so often used in this paper. The thickening is essentially produced by the subendothelial layer which appears very cellular.

It would be well to point out that the thickness of the intima in this group of children (Table I) is often much greater than that commonly reported as normal. My measurements gave from 10 to 15 microns in transverse frozen sections mounted in gelatin. Langhaas,[11] for example, gives 0.015 mm. to 0.025 mm. as the normal for three children, 4 days, 1½ years and 10 years old respectively, and Thoma [2] 30, 35 and 41 microns for a child 7 weeks old. Text-Fig. 1


Ascending aorta
Transverse aorta
Thoracic aorta
Abdominal aorta
Abdominal aorta
Age of Patients 2d 14d 6w 7w 2m 2½m 3½m 4m 5m 6m 7m 7m 7½m 18m 21m 3y 4y 5y 6y 10y
Patients 259 261 253 263 246 254 1 256 261 260 240 264 255 244 248 252 241 252 248 245

TEXT-FIGURE 1

Graphic representation of Table I showing the distribution of thickness over 100 microns

is a graphic representation based on Table I of the distribution along the aorta of portions in which the thickness of the intima is over 100 microns. From this figure it may be seen how wide the variations are, either in the same subject or in a group of children of different ages.

These data do not agree with the view generally accepted that, if in the newborn the intima is very thin, it increases in thickness gradually and regularly with age, presenting a more or less constant thickness for each age. On the contrary, it seems that during childhood, as the subject is actively growing, the intima presents a variable thickness, which is often considerable and exceeds 200 microns

even in very young subjects (Case 253). Such thickened portions, however, have a varied distribution along the aorta (Table I and Text-Fig. 1). They do not represent, therefore, a regular and more advanced growth of the intima, neither are they more marked in a particular segment of the aorta. In Case 253, an infant 6 weeks old, a great thickening is found in the upper abdominal aorta (Table I), while this is not observed in Case 246, an infant 2 months old. It is

TABLE I

Thickness in Microns of the Intima of the Aorta in a Group of Children between the Ages of 2 Days and 10 Years

Patient	Age	Sex	Ascending aorta	Transverse aorta	Thoracic aorta	Upper abdominal aorta	Lower abdominal aorta
259	2 d.	M					
251	14 d.	F					
253	6 w.	F		60–160	80–120	90–210	
263	7 w.	M			40	40–90	20–160
246	2 m.	M				35	25–70
254	2½ m.	F		130–255	60–220	40–135–250	20–70–290
1	3½ m.	M	65		60–110	25–105	35–75
265	4 m.	F			30–70	35	60
261	5 m.	M			65–245	80–110	40–75–225
260	5 m.	F	85	40–85–210	50–200	35–85	35–65
240	7 m.	F	40		50	50	30
264	7 m.	M	115		50–100	40–50	40–180
255	7½ m.	F			40–90	15–130	40–100–140
244	18 m.	F	25	50	95–210	75–100	35
248	21 m.	F			65–170	165	20–75
252	3 y.	M	20–40		30–60	40–60	45–110
241	4 y.	M				25–60	30–40–115
262	5 y.	F	180		65–110	50–80	60–110
238	6 y.	F	80–100	110	90	30–175	35–190
245	10 y.	M			70	35–150	35–65

present in children 6 weeks old, $2\frac{1}{2}$, $3\frac{1}{2}$, 5, 7, $7\frac{1}{2}$, 18 and 21 months old, and 3, 4, 5, 6 and 10 years old (Table I), either in the transverse, thoracic and upper and lower abdominal aorta at the same time (Case 254); at the transverse, thoracic and upper abdominal aorta (Case 253); at the thoracic, and upper and lower abdominal aorta (Case 261); at the transverse and thoracic aorta (Case 260); at the ascending, thoracic and lower abdominal aorta (Cases 264 and 262); at the upper and lower abdominal aorta (Case 255); or only at the upper (Case 245), or lower abdominal aorta (Cases 263, 252 and 241). On the other hand it is lacking in infants 2, 4 and 7 months old (Cases 246, 265 and 240 — Table I and Text-Fig. 1).

One gains the impression that these thickenings, instead of being permanent and representing in a particular subject the normal thickness of the intima at such an age, are in fact transient. They tend to disappear soon after being formed and as the child grows up, reappearing, however, later on in the same individual when the conditions giving rise to them are again met with. This, in all probability, would be reproduced several times during infancy in the same subject.

This assumption is corroborated in the study of the location and the structure of the sloping overgrowths in children of this group. Well marked and cellular sloping overgrowths, indicating a process which is actually going on, appear in Cases 254, 261, 241 and 238, children respectively $2\frac{1}{2}$ months, 5 months, 4 years and 6 years old, presenting a similar structure in all of them. This suggests a periodic recurrence of developmental thickenings in childhood. Their absence, or at least their non-existence as structures with well defined microscopic features, in Cases 264, 255 and 262, children respectively 7 months, $7\frac{1}{2}$ months and 5 years old, suggests that they may be transient rather than permanent morphological features in the aorta of infants.

In some cases sloping overgrowths are found in more than one portion of the aorta at the same time, and are lacking in intermediate portions. This suggests different and independent stages of a peculiar phenomenon occurring synchronously at different places in the same aorta. Again indefinite sloping overgrowths are noticed in other cases, as if the intermediary stages of such thickenings were just appearing or disappearing. This is in accordance with the idea of transient and recurrent morphological changes in infancy.

TABLE II

Thickness in Microns of the Tunica Media of the Aorta in a Group of Children between the Ages of 2 Days and 10 Years

Patient	Age	Sex	Ascending aorta	Transverse aorta	Thoracic aorta	Upper abdominal aorta	Lower abdominal aorta
259	2 d.	M	890	725	625	560	400
251	14 d.	F	875	750	590	500	250
253	6 w.	F		580	650	610	350–450
263	7 w.	M	650–1080	790	500	500	460–550
246	2 m.	M	810	800	650	410–650	460
254	2½ m.	F	1470	1540	760	550–660–820	450–530
1	3½ m.	M	680		580	360	380
265	4 m.	F	950	950	430–540	490	570
261	5 m.	M		910	490–560	500–540	400
260	5 m.	F	940	600	600	500	380
240	7 m.	F	1000	800–980	640	480	420
264	7 m.	M	560–840	800–920	470–560	420	350–370
255	7½ m.	F	1000	920	650	590	520
244	18 m.	F	810	750	505	590	450
248	21 m.	F			480	600	480
252	3 y.	M	900	750	570	500	450–600
241	4 y.	M	800–1110	1140	760	620	600
262	5 y.	F	1450	770	560	490	480
238	6 y.	F	1040	1000	640	550	600
245	10 y.	M	700	1550–1800–1900	670	750	630

Why in childhood does a transient thickening develop in the intima of the aorta? In Table III are tabulated the circumferences of the thoracic and abdominal aorta as measured in some of the specimens preserved in formalin. In order to afford, as far as possible, a comparative study of such data in a group of children of different ages, in every case identical portions were selected, namely the mouths of the fourth pair of intercostal arteries and of the celiac axis.

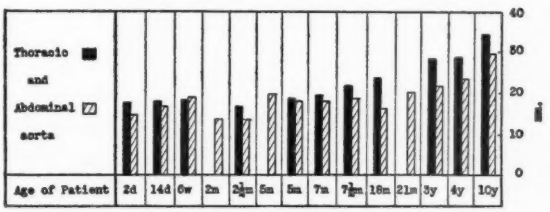
Curious variations are demonstrable in the rate of growth of the circumferences of the thoracic and upper abdominal aorta, as seen in Text-Fig. 2, which is a graphic representation of Table III.

TABLE III

Circumference in mm. of the Thoracic and Upper Abdominal Aorta in a Group of Children between the Ages of 2 Days and 10 Years

Thoracic aorta	17	17.5	18		16.5		18.5	19.5	21.5	23.5		28	28.5	34
Abdominal aorta	14.5	16.5	18.5	13	13	19.5	18	18	18.5	16	20	21.5	23.5	29.5
Age of Patients	2 d.	14 d.	6 w.	2 m.	2½ m.	5 m.	5 m.	7 m.	7½ m.	18 m.	21 m.	3 y.	4 y.	10 y.
Patient	259	251	253	246	254	261	260	240	255	244	248	252	241	245

While at 2 and 14 days of age the circumference of the upper abdominal aorta is less than that of the thoracic aorta, at 6 weeks it is a little greater, being again less at 2½ months. At 7 and 7½ months, the rate between the two circumferences is more or less similar to that noted at 2 and 14 days, and becomes considerably less in the abdominal aorta at 18 months, and this difference is maintained, though not so marked, at 3, 4 and 10 years of age. Sometimes the



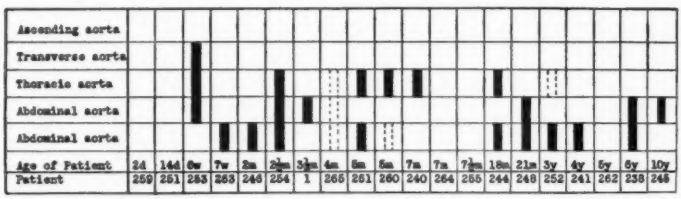
TEXT-FIGURE 2

Graphic representation of Table III

circumference of the thoracic and the upper abdominal aorta increases more or less regularly. At other times, that of the abdominal aorta grows more rapidly, almost reaching that of the thoracic; while at still other times the growth of the thoracic portion is considerably more rapid than that of the abdominal. Later it becomes slower again as compared with that of the upper abdominal aorta.

Evidence is therefore available, suggesting that the growth of the aorta does not proceed in a regular and uniform way throughout the vessel. Sometimes the abdominal aorta increases more rapidly than the thoracic. At other times the reverse takes place, but a constant rate is never maintained. This phenomenon also would take place during the active growth of the subject, and probably is reproduced several times in the same individual.

With regard to this view one must consider, furthermore, the close relation between the growth of the aorta and that of the bony structures. It becomes obvious that developmental changes will be more marked in the descending and abdominal than in the ascending and transverse aorta. It is curious to note that Text-Fig. 3, which is a graphic representation of the distribution of sloping overgrowths in the different portions of the aorta, as they appear in this group of children, agrees in a general way with Text-Fig. 1, which represents the distribution of thicknesses over 100 microns. The


Ascending aorta
Transverse aorta
Thoracic aorta
Abdominal aorta
Abdominal aorta
Age of Patient 2d 14d 6w 7w 2m 2½m 3½m 4m 6m 6m 7m 7m 7½m 18m 21m 3y 4y 5y 6y 10y
Patient 259 261 263 263 246 254 1 265 261 260 240 264 255 244 248 252 241 262 238 246

TEXT-FIGURE 3

Graphic representation of the distribution of sloping overgrowth of the intima in the aorta of a group of children of different ages

two findings correspond and may be explained as developmental but transient thickenings of the subendothelial layer taking place periodically in several and different portions of the aorta.

This may occur: (*a*) when the growth is more rapid in the subendothelial layer of the vessel than in the vessel as a whole; (*b*) when the rate of growth between two adjoining portions of the aorta is altered so that one grows more rapidly than the other. In both cases a thickening of the subendothelial layer will be produced which is, however, transient and discontinuous in the length of the vessel and tends to be reabsorbed as the rate of growth changes at that point.

No normal children, of course, were examined. Most of them were undernourished infants, often with a history of gastro-intestinal

disturbances and infectious disease. In Case 253, for example, a girl 6 weeks old, who developed a cerebral abscess following an infected spina bifida, and in whom the infectious process was present during practically all of her extra-uterine life, marked and extensive thickenings of the intima were found. They were less marked in Case 264, a well developed and well nourished 7 months old baby dying of leptomeningitis after eight days of illness. But, on the other hand, they were also quite distinct in another well developed and well nourished baby (Case 252), 3 years old, dying of diphtheria on the fifth day of illness.

Why do the sloping overgrowths develop just at the posterior border of the descending aorta? Robertson [12] demonstrated that the vascularization is different in the ascending aortic limb and in the descending thoracic portion of the aorta. While an anastomosing circle of vessels exists in the ascending aortic limb, so that the vascularization is assured in a more or less uniform manner at the front, back and lateral portions of the aorta, this is not the case with the descending thoracic aorta. In the latter the vasa vasorum are most numerous along two longitudinal strips just lateral and parallel to the efferent vessels, so that the vascularization is distinctly more developed at the back than at the front and lateral parts. It is obvious that the subendothelial layer of the intima will show a tendency to increase more quickly in the better-nourished portions of that coat, a direct relation existing between growth of connective tissue and the blood supply. Apparently, as a developmental change, this becomes particularly prominent during infancy.

In thirteen of the twenty cases, I found fatty changes in the intima. In a few instances they presented no relation to developmental thickenings (Cases 264, 255, 262 and 245). Fat occurs more or less uniformly throughout the lining endothelial cells, or as extra-cellular fine droplets along the elastica interna. More often, however, fat occurred in the form of anisotropic droplets (lipoid degeneration) in star-shaped and fusiform cells more or less abundant in the subendothelial layer.

In Cases 263, 254, 1, 261 and 240, fatty and lipoid degenerations were more marked and sometimes sharply limited to the sloping overgrowths. The degenerative processes appeared focally in the aorta in the same localities in which fatty streaks and early arteriosclerotic changes later became predominant. Possibly such focal dis-

tribution is the result of a local disturbance of the blood supply. As a matter of fact, one should expect a more uniform distribution if these were the result of toxemia alone. In Cases 246, 244, 248, 252, 241 and 238, no fatty changes were found, while quite marked sloping overgrowths existed in some of them.

This brings forth the question of juvenile arteriosclerosis. The aorta of Case 240 was the first examined, and after a comparative study of sections from various parts of the aorta a diagnosis of arteriosclerosis was made on the presence of a subendothelial thickening of the intima with some fatty change. This diagnosis seemed logical until I examined seventeen other children dying from diverse infectious and nutritional diseases, finding very similar changes. Transient pachymenia of the intima, therefore, merits consideration as a pitfall in the diagnosis of juvenile arteriosclerosis in infants.

Another pathological finding was a peculiar degeneration of the chromotropic connective tissue. In some places it appears increased in amount and presents a flocculent aspect. The metachromatic color reaction suggests a close relationship with mucoid material, as well as of the chromotropic substance itself. However, in some investigations preceding those of Björling [13] and of Schultz,[14] the chromotropic connective tissue was considered and described as mucoid degeneration, inasmuch as it was then generally assumed that the normal connective tissue of the vessel did not give the reaction for mucin.

In order to avoid a misunderstanding in regard to the peculiar change above referred to, the term flocculation has been employed. Flocculation (mucoid degeneration, hyaline degeneration) of the chromotropic substance is better evidenced in frozen sections stained by cresyl violet. It is completely overlooked in ordinary sections of material embedded in paraffin and stained by hematoyxlin-eosin. Therefore, while metachromasia of the vascular connective tissue may be made apparent in paraffin sections, as Schultz has pointed out, such is not the case with the delicate pathological change above described.

The study of frozen sections by the Schultz stain suggests that in childhood the elastic substance is not deposited at the same time in all portions of the elastic tissue of the aorta. At first it is manifest in small, irregular segments (Figs. 1 and 7) which have lost their meta-

chromatic color reaction. As other segments in the same membrane retain their original metachromasia, a discontinuous appearance is obtained. Elastic membranes in which the elastic substance is incompletely formed were more abundant in the internal and external than in the middle portions of the media (Fig. 7) and more abundant in the ascending and transverse than in the thoracic and abdominal aorta. The elastica interna presents a discontinuous aspect (Fig. 1) in all the children examined, and its internal surface is more or less irregular. Such appearances are related to the age: the younger the subject, the more marked the granulation (compare Figs. 1 and 7).

Summary and Conclusions

In childhood the intima of the aorta presents a variable thickness in the same subject, if complete transverse sections from the ascending, transverse, thoracic and abdominal aorta are examined.

At the posterior part of the aorta, the intima often measures more than 100 microns in thickness, resulting from the presence of a cellular subendothelial layer. The thickened portions of the intima, however, do not rise above the surface of the vessel, so that they cannot be detected macroscopically. The intima in transverse sections becomes gradually thickened, until a maximum is attained in its posterior portion. Beyond this, it again becomes gradually attenuated and terminates in tapering ends as the subendothelial layer disappears. The peculiar aspect is referred to as "sloping overgrowths" of the intima.

A comparative study of such changes in a group of twenty children between the ages of 2 days and 10 years suggests that they correspond to transient and recurrent developmental changes. They were regularly found in eighteen children, lacking only in two infants, 2 and 14 days old.

These postnatal developmental changes do not present any definite relation to the age of the subject, to the location in the aorta or to degenerative and non-specific inflammatory processes.

It is assumed that they are not permanent but transient physiological changes, so that quite marked thickenings (*pachymenia*) of the intima tend to disappear soon after they are produced and as the growth of the aorta proceeds. At the same time others arise in other portions of the vessel. It seems likely that these reactions are reproduced many times in the same subject.

Differences in the rate of growth between the subendothelial layer and the vessel as a whole, and between two adjoining portions of the aorta, appear to be the chief factors in the production of the transient pachymenia of the intima in infancy.

These results also confirm the frequency, in children, of fatty changes in some localities of the aorta, namely, the mouth of the intercostal arteries and the ascending and the abdominal aorta, previously reported by Oppenheimer,[15] Klotz and Manning,[10] Stumpf,[9] Klotz,[16, 17] Schmidtmann,[18] Zinserling,[19] Kube and Ssolowjew,[20] and others. They show, moreover, that flocculation (mucoid degeneration) of the chromotropic connective tissue, involving especially the internal portions of the media in the ascending and transverse aorta, is another finding in infants dying from infectious diseases, and that fatty and lipoid degeneration may occur focally in connection with a dorsal connective tissue or developmental plaque.

Developmental changes associated with degenerative processes are a pitfall in the diagnosis of juvenile arteriosclerosis in infancy. In some children fatty changes were seen in the absence of developmental thickenings of the intima, and in others, on the contrary, quite marked simple developmental changes were found in the absence of degenerative processes.

In conclusion, the writer wishes to express his thanks to Professor Oskar Klotz for much helpful advice and guidance during the progress of this work in the Department of Pathology of the University of Toronto.

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DESCRIPTION OF PLATE

All figures were drawn with camera lucida. Only the homogeneous greenish segments containing elastic substance are represented in each elastic membrane in Figs. 1 and 7. The outlines of the coats of the aorta and the elastica interna are the only structures represented in Figs. 2, 3, 4, 5, 6, 8 and 9. I = intima; M = tunica media; Ei = elastica interna.

PLATE 83

FIG. 1. Case 259, infant 2 days old. Elastic tissue (Schultz' stain) in thoracic aorta; a = elastica interna; b = elastic membrane from the middle of the media; c = elastic membrane from the external portion of the media.

FIG. 2. Case 263, infant 7 weeks old. Complete transverse section of the abdominal aorta 3 mm. above the origin of the common iliacs. The subendothelial layer becomes gradually thicker, reaching a maximum at the back part of the vessel. This dorsal thickening of the intima is referred to as "sloping overgrowth."

FIG. 3. Case 254, infant 2½ months old. Sloping overgrowth at the back part of the thoracic aorta between the fourth and fifth pair of intercostal arteries.

FIG. 4. Case 254, infant 2½ months old. Marked sloping overgrowth in the back part of the abdominal aorta at the mouth of the left renal artery. In this complete transverse section, the subendothelial layer appears discontinuous and the thickenings usually present near the mouth of a branch form a structure quite apart from the dorsal connective tissue plaque.

FIG. 5. Case 254, infant 2½ months old. In this complete transverse section of the abdominal aorta 5 mm. above the common iliacs, the subendothelial layer is continuous, forming a marked sloping overgrowth at the back part.

FIG. 6. Case 261, infant 5 months old. The edge and initial portion of three sloping overgrowths are represented, one, the most marked, at the thoracic aorta (a); another, less marked, at the upper abdominal aorta (b); and still another at the lower abdominal aorta (c).

FIG. 7. Case 261, infant 5 months old. Elastic tissue in thoracic aorta (Schultz' stain); a = elastic interna; b = elastic membrane from the internal portion; c and d = middle portion; and e = external portion of the media.

FIG. 8. Case 248, infant 21 months old. Sloping overgrowth at the back part of the upper abdominal aorta (mouth of the celiac axis).

FIG. 9. Case 262, child 5 years old. At the thoracic aorta, the intima presents a subendothelial layer of more or less uniform thickness.

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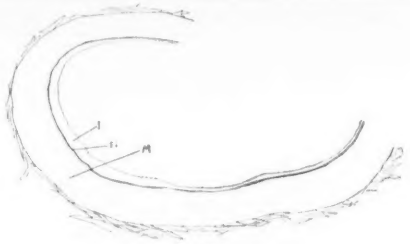

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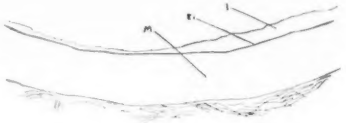

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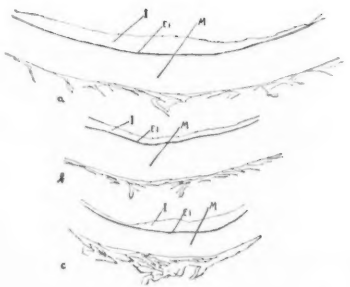

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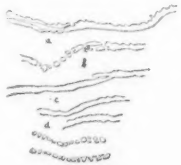

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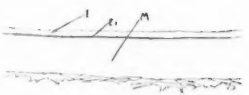

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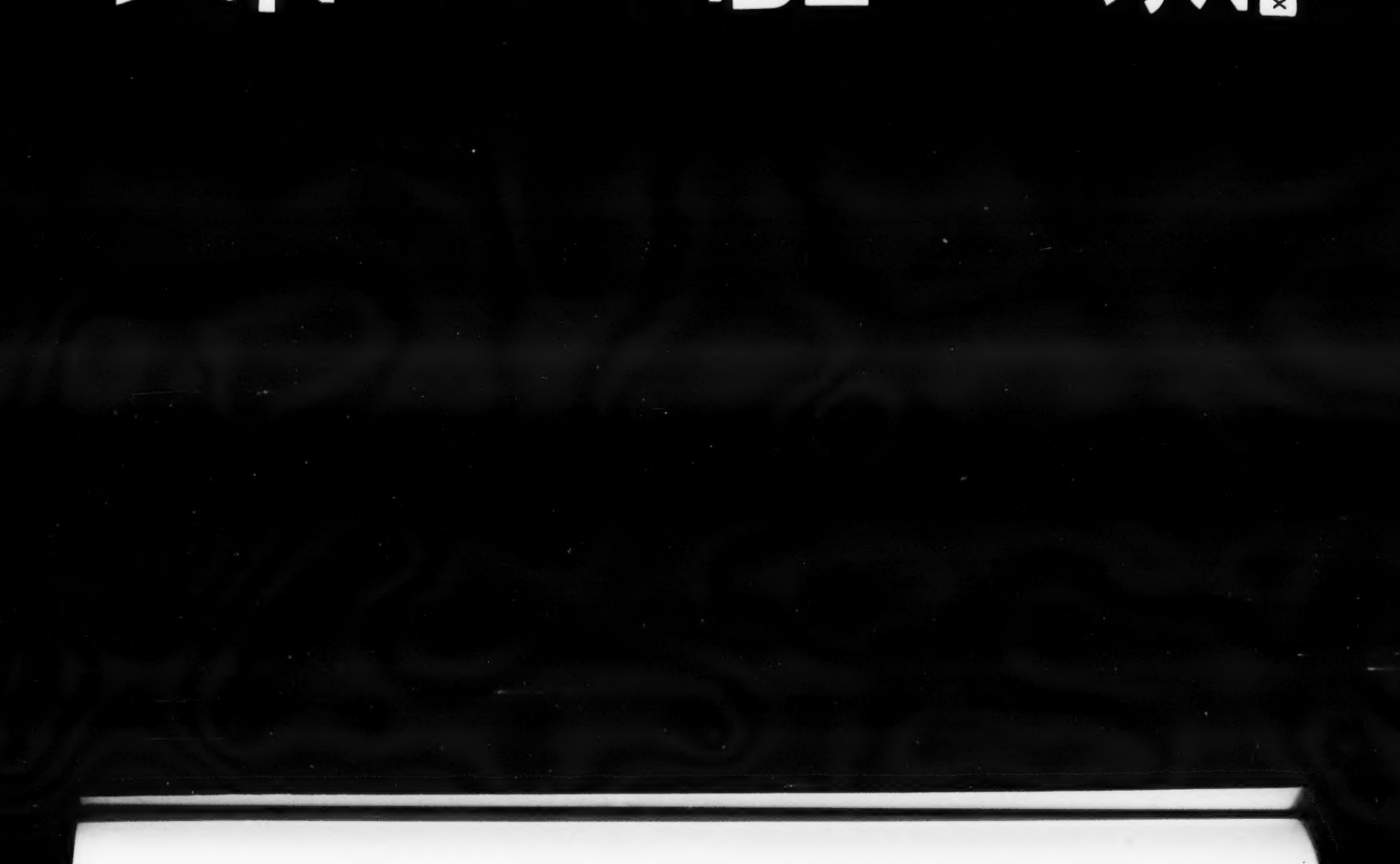
Transient Pachymenia of Intima of Aorta